Product Monograph

Including Patient Medication Information

[Pr]VANFLYTA®

Quizartinib tablets

For oral use

17.7 mg and 26.5 mg quizartinib (as quizartinib hydrochloride)

Antineoplastic Agent

Daiichi Sankyo Pharma Canada Ltd.

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Toronto, Ontario

Canada

M5X 1E3

Date of Authorization:
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Recent Major Label Changes

Not applicable

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

VANFLYTA (quizartinib) is indicated:

- in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA maintenance monotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) positive.

  Improvement in overall survival has not been demonstrated for maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (see 14.1 Clinical Trials by Indication).

  A validated test is required to confirm the *FLT3*-ITD status of AML.

1.1. Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (>65 years): Evidence from clinical studies suggests that differences in safety were observed in the geriatric population (see 7.1.4 Geriatrics).

2. Contraindications

VANFLYTA is contraindicated in patients:

- with congenital long QT syndrome or with a history of ventricular arrhythmias or torsades de pointes (see 7 Warnings and Precautions, Cardiovascular).
- With severe uncorrected hypokalemia or hypomagnesemia (see 7 Warnings and Precautions, Cardiovascular).
- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.

3. Serious Warnings and Precautions Box

- VANFLYTA can prolong the QT interval (see 10.2 Pharmacodynamics). Torsades de pointes, cardiac arrest, and sudden death have been reported in patients receiving VANFLYTA (see 7 Warnings and Precautions, Cardiovascular, and 8 Adverse Reactions). Electrocardiograms (ECGs) should be performed, and electrolyte abnormalities should be corrected before initiating VANFLYTA treatment. Do not initiate VANFLYTA therapy if the QT interval corrected by Fridericia's formula (QTcF) is greater than 450 ms or in patients with severe hypokalemia, hypomagnesemia, or

long QT syndrome. Monitor ECGs and electrolyte levels during treatment. VANFLYTA dosage adjustment may be required in the event of QT prolongation. Reduce the VANFLYTA dose when used concomitantly with strong CYP3A4/5 inhibitors (see 2 Contraindications, 4.2 Recommended Dose and Dosage Adjustment and 7 Warnings and Precautions, Cardiovascular).

4. Dosage and Administration

4.1. Dosing Considerations

Select patients for the treatment of AML with VANFLYTA based on the presence of *FLT3*-ITD mutation (see 14.1 Clinical Trials by Indication).

VANFLYTA should be initiated only if QTcF is less than or equal to 450 ms (see 7 Warnings and Precautions, Cardiovascular).

During induction and consolidation, electrocardiograms (ECGs) should be performed prior to initiation and then once weekly during VANFLYTA treatment or more frequently as clinically indicated (see 7 Warnings and Precautions, Cardiovascular).

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 dose should be escalated only if QTcF is less than or equal to 450 ms (see Table 1 and 7 Warnings and Precautions, Cardiovascular).

Electrolyte abnormalities (hypokalemia and hypomagnesemia) should be corrected, and if possible, concomitant administration of drugs that prolong the QT interval should be avoided (see 7 Warnings and Precautions, Cardiovascular).

4.2. Recommended Dose and Dosage Adjustment

Treatment with VANFLYTA should be initiated by a physician experienced in the use of anticancer therapies.

Recommended Dose

VANFLYTA should be administered in combination with standard chemotherapy at a dose of 35.4 mg (2 x 17.7 mg) once daily for two weeks in each cycle of induction. For patients who achieved complete remission (CR) or complete remission with incomplete hematologic recovery (CRi), VANFLYTA should be administered at 35.4 mg once daily for two weeks in each cycle of consolidation chemotherapy followed by VANFLYTA maintenance monotherapy initiated at 26.5 mg once daily. After two weeks the maintenance dose should be increased to 53 mg (2 x 26.5 mg) once daily if the QT interval corrected by Fridericia's formula (QTcF) is less than or equal to 450 ms (see Table 2 and 7 Warnings and Precautions, Cardiovascular).

For additional dosing information, see Table 1, Table 2 and Table 3.

Table 1: VANFLYTA 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 (2 x 17.7 mg) once daily	35.4 mg (2 x 17.7 mg) once daily	• Starting dose of 26.5 mg once daily for two weeks if QTcF is less than or equal to 450 ms • After two weeks, if QTcF is less than or equal to 450 ms, the dose should be increased to 53 mg (2 x 26.5 mg) once daily.
Duration (28-day cycles)	Two weeks (Day 8 to 21) in each cycle	Two weeks (Day 6 to 19) 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.

See 14 Clinical Trials for Chemotherapy dosing during the QuANTUM-First study.

For patients who proceed to hematopoietic stem cell transplantation (HSCT), VANFLYTA should be stopped 7 days before the start of a conditioning regimen. VANFLYTA may be resumed after completion of the transplant based on white blood cell count (WBC) and at the discretion of the treating physician for patients with sufficient hematologic recovery and with less than or equal to Grade 2 graft-versus-host disease (GVHD), not requiring the initiation of new systemic GVHD therapy within 21 days, following the dosing recommendations described above.

Dose Modifications

The recommended dose modifications guidelines for adverse reactions are listed in Table 2.

Table 2: Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	Recommended Action
QTcF between 450 and 480 ms (Grade 1)	• Continue VANFLYTA dose.
QTcF greater than 480 ms and less than or equal to 500 ms (Grade 2)	• Reduce VANFLYTA dose (see Table 3 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.

Adverse Reaction	Recommended Action
QTcF greater than 500 ms (Grade 3)	• Interrupt VANFLYTA. • Resume VANFLYTA at a reduced dose (see Table 3) when QTcF returns to less than 450 ms. • Do not escalate to 53 mg once daily during maintenance if QTcF greater than 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 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 non-hematologic adverse reactions	• Interrupt VANFLYTA. • Resume treatment at the previous dose if adverse reaction improves to less than or equal to Grade 1. • Resume treatment at a reduced dose (see Table 3) if adverse reaction improves to less than Grade 3. • Discontinue if Grade 3 or 4 adverse reaction persists beyond 28 days and is suspected to be associated with VANFLYTA.
Persistent Grade 4 neutropenia or thrombocytopenia without active bone marrow disease	• Reduce the dose (see Table 3).

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

Table 3: Dose Adjustments for Adverse Reactions by Phase during Treatment with VANFLYTA

Phase of Treatment	Full Dose	Dose Reduction
Induction or Consolidation	35.4 mg	26.5 mg
Maintenance (First two weeks)	26.5 mg	Interrupt
Maintenance (After two weeks)	53 mg	35.4 mg

Concomitant use with strong cytochrome P450 enzyme (CYP3A4/5) inhibitors may increase quizartinib exposure. If concomitant use of a strong CYP3A4/5 inhibitor is unavoidable, reduce the dose of VANFLYTA as shown in Table 4. After discontinuation of the strong CYP3A4/5 inhibitor, resume VANFLYTA at the original dose (see 9.4 Drug-Drug Interactions).

The recommended dose reductions when VANFLYTA is used concomitantly with strong CYP3A4/5 inhibitors are listed in Table 4.

Table 4: Dosage Adjustments for Concomitant Use with Strong CYP3A4/5 Inhibitors

Full Dose	Dose Reductions for Concomitant Use with Strong CYP3A4/5 Inhibitors
26.5 mg	17.7 mg
35.4 mg	
53 mg	26.5 mg

Treatment with VANFLYTA should be interrupted in patients receiving the 17.7 mg dose and requiring treatment with a strong CYP3A4/5 inhibitor.

Special Populations

Pediatrics (≤ 18 years)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years)

No dose adjustment of VANFLYTA is required in patients aged 65 years or older (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions).

Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment.

VANFLYTA is not recommended for use in patients with severe renal impairment (creatinine clearance [CLcr] <30 mL/min, estimated by Cockcroft-Gault) as safety and efficacy have not been evaluated in this population (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Hepatic Impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment.

VANFLYTA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C or total bilirubin >3 times ULN and any value for AST) as safety and efficacy have not been evaluated in this population (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

4.4. Administration

VANFLYTA should be taken orally at approximately the same time each day and may be taken with or without food. Swallow tablets whole. Do not cut, crush, or chew the tablets.

4.5. Missed Dose

Missed Dose or Vomiting

If a dose of VANFLYTA is missed or not taken at the usual time, the patient should take the dose as soon as possible on the same day and return to the usual schedule the following day. The patient should not take two doses on the same day.

If the patient vomits after taking VANFLYTA, the patient should not take an additional dose that day. The patient should take the next dose the following day at the usual time.

5. Overdose

There is no known antidote for overdoses of VANFLYTA. In the event of an overdose, interrupt treatment, perform an ECG to monitor for QT interval prolongation (see 4.2 Recommended Dose and Dosage Adjustment and 7 Warnings and Precautions, Cardiovascular), and give appropriate supportive measures.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 5: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral use	Tablets, 17.7 mg and 26.5 mg quizartinib (as quizartinib hydrochloride)	Ferric oxide yellow (26.5 mg only), hypromellose, hydroxypropyl betadex, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide, triacetin

Description

VANFLYTA 17.7 mg tablets

A white, round, tablet, debossed with "DSC511." Each tablet contains 17.7 mg quizartinib (as quizartinib hydrochloride).

VANFLYTA 26.5 mg tablets

A yellow, round, tablet, debossed with "DSC512." Each tablet contains 26.5 mg quizartinib (as quizartinib hydrochloride).

Packaging:

Aluminium blisters with 14 tablets per blister card in a carton containing 1, 2 or 4 blister cards.

7. Warnings and Precautions

Carcinogenesis and Genotoxicity

See 16 Non-Clinical Toxicology.

Cardiovascular

QT Interval Prolongation, Torsades de Pointes, and Cardiac Arrest

VANFLYTA prolongs the QT interval in a dose- and concentration-dependent manner (see 10.2 Pharmacodynamics). Torsades de pointes, cardiac arrest, and sudden death have been reported in patients receiving VANFLYTA (see 8 Adverse Reactions). The quizartinib development program excluded patients with a QTcF ≥450 ms or other factors that increased the risk of QT prolongation or arrhythmic events (e.g., New York Heart Association Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome, history of second- or third-degree heart block, myocardial infarction within 6 months, uncontrolled angina pectoris, uncontrolled hypertension).

VANFLYTA is contraindicated in patients with congenital long QT syndrome, with a history of ventricular arrhythmias or torsades de pointes, or with severe uncorrected hypokalemia or hypomagnesemia (see 2 Contraindications). VANFLYTA should be used with caution in patients who are at risk of developing QT interval prolongation, including patients with uncontrolled or significant cardiovascular disease, and patients receiving concomitant drugs 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 QTcF interval is greater than 450 ms. Electrolytes should be maintained in the normal range (see 4.1 Dosing Considerations).

During induction and consolidation, ECGs should be performed prior to initiation and then once weekly during VANFLYTA 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).

Permanently discontinue VANFLYTA in patients who develop QT interval prolongation with signs or symptoms of life-threatening arrhythmia (see 4.2 Recommended Dose and Dosage Adjustment).

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.

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

ECG Monitoring with QT Interval Prolonging Medicinal Products

Patients should be monitored more frequently with ECGs if coadministration of VANFLYTA with medicinal products known to prolong the QT interval is required. Examples of QT prolonging drugs include but are not limited to antifungal azoles, ondansetron, granisetron, azithromycin, pentamidine, doxycycline, moxifloxacin, atovaquone, prochlorperazine, and tacrolimus.

Concomitant Use with Strong CYP3A4/5 Inhibitors

Concomitant use with strong CYP3A*4/5* inhibitors may increase quizartinib exposure, and therefore, the dose of VANFLYTA should be reduced (see 4.2 Recommended Dose and Dosage Adjustment and 9.4 Drug-Drug Interactions).

Reproductive Health

- **Fertility**

There are no human data on the effect of VANFLYTA on fertility. Based on findings in animals, female and male fertility may be impaired with treatment with VANFLYTA (see 16 Non-Clinical Toxicology).

7.1. Special Populations

7.1.1. Pregnancy

There are no data on the use of quizartinib in pregnant women. Based on findings in animals, VANFLYTA may cause embryo-fetal toxicity when administered to pregnant women (see 16 Non-Clinical Toxicology).

VANFLYTA should not be used during pregnancy. Pregnant women should be advised of the potential risk to the fetus.

Women of childbearing potential should undergo pregnancy testing before starting treatment with VANFLYTA.

Based on findings in animals, VANFLYTA may cause embryo-fetal harm when administered to a pregnant woman (see 16 Non-clinical Toxicology). Advise pregnant women of the potential risk to the fetus. Advise women of reproductive potential to use effective contraception during treatment with VANFLYTA and for at least 7 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with VANFLYTA and for at least 4 months after the last dose.

7.1.2. Breastfeeding

It is unknown whether quizartinib or its active metabolites are excreted in human milk. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with VANFLYTA and for at least 5 weeks after the last dose.

7.1.3. Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Of the 533 patients with newly diagnosed AML in the QuANTUM-First study 134 (25.1%) were 65 years of age and older, while 2 (0.4%) were 75 years of age. A higher incidence of fatal infections was reported in patients 65 years of age and older, compared to younger patients (13% vs. 5.7%), especially in the early treatment period. Discontinuations were reported in 29% of patients 65 years of age and older, and in 16.4% of younger patients.

Clinical studies of VANFLYTA did not include sufficient numbers of patients 75 years of age and older to determine whether they respond differently from younger adult patients.

8. Adverse Reactions

8.1. Adverse Reaction Overview

In QuANTUM-First, the phase III, randomized, placebo-controlled trial of VANFLYTA in patients with newly diagnosed *FLT3*-ITD positive AML, the most common adverse reactions (incidence ≥20%) in the VANFLYTA arm were febrile neutropenia, diarrhea, nausea, sepsis, abdominal pain, neutropenia, headache and vomiting. The most common Grade 3 or 4 adverse reactions (incidence ≥5%) were febrile neutropenia, sepsis, neutropenia, thrombocytopenia, fungal infections, and anemia.

The most common serious adverse reactions (incidence ≥2%) in the VANFLYTA arm were febrile neutropenia (11%), neutropenia (3.0%), fungal infections (2.3%) and herpes infections (2.3%). Adverse reactions with a fatal outcome were sepsis (5.0%), fungal infections (0.8%) and cardiac arrest (0.4%).

The most common adverse reactions (incidence ≥2%) associated with dose interruption of VANFLYTA were neutropenia (10.6%), thrombocytopenia (4.5%) and electrocardiogram QT prolonged (2.6%). The most common adverse reactions (incidence ≥2%) associated with dose reduction of VANFLYTA were neutropenia (9.1%), thrombocytopenia (4.5%) and electrocardiogram QT prolonged (3.8%).

The most common adverse reactions (incidence ≥1%) associated with permanent discontinuation of VANFLYTA were sepsis (5%) and thrombocytopenia (1.1%).

Safety Profile During Maintenance Monotherapy

During the maintenance monotherapy phase of QuANTUM-First, the most common adverse

reactions in the VANFLYTA arm were neutrophil count decreased (87.9%), platelet count decreased (72.4%), hemoglobin decreased (55.2%), alanine aminotransferase increased (49.1%), upper respiratory tract infections (27.6%), nausea (23.3%) and diarrhea (20.7%). The most frequent Grade 3 or 4 adverse reactions with VANFLYTA were neutrophil count decreased (71.6%), platelet count decreased (24.1%) and hemoglobin decreased (18.1%).

The most common serious adverse reactions in the VANFLYTA arm were herpes infections (3.4%), neutropenia (2.6%), upper respiratory tract infections (1.7%) and vomiting (1.7%). No fatal adverse reactions occurred during maintenance.

The most common adverse reactions associated with dose interruption of VANFLYTA were neutropenia (24.1%), thrombocytopenia (10.3%) and electrocardiogram QT prolonged (4.3%). The most common adverse reactions associated with dose reduction of VANFLYTA were neutropenia (20.7%), thrombocytopenia (10.3%) and electrocardiogram QT prolonged (5.2%). The most common adverse reactions associated with permanent discontinuation of VANFLYTA were thrombocytopenia (2.6%), nausea, neutropenia and decreased appetite (1.7% each).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The safety of VANFLYTA was investigated in QuANTUM-First, a randomized, double-blind, placebo-controlled trial in adult patients with newly diagnosed *FLT3*-ITD positive AML. Patients were treated with VANFLYTA (N=265) or placebo (N=268) in combination with standard chemotherapy, followed by VANFLYTA maintenance monotherapy (see 14 Clinical Trials). The overall median duration of therapy was 10.7 weeks (range: 0.1 to 184.1) for patients in the VANFLYTA arm versus 9.5 weeks (range: 0.4 to 181.9) for patients in the placebo arm. In QuANTUM-First, 116 (43.8%) of patients in the VANFLYTA arm and 92 (34.3%) patients in the placebo arm entered the maintenance monotherapy treatment phase. The median duration of therapy for maintenance was 67.4 weeks (range: 0.4 to 167.0) for patients in the VANFLYTA arm versus 67.7 weeks (range: 0.3 to 167.4) for patients in the placebo arm.

Table 6 presents adverse reactions reported in ≥10% of VANFLYTA-treated patients in the QuANTUM-First Clinical Study.

Table 6: Adverse Reactions Reported in ≥10% of VANFLYTA-Treated Patients in Quantum-First Study (Safety Analysis Set)

System Organ Class / preferred term	VANFLYTA + Standard Chemotherapy N=265		Placebo + Standard Chemotherapy N=268	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and Lymphatic System Disorders				
Febrile neutropenia[a]	44.2	43.4	42.2	41.0
Neutropenia[b]	29.1	26.0	14.2	11.9
Thrombocytopenia[c]	17.7	12.8	13.4	11.6
Anemia	10.9	5.7	7.1	5.2
Gastrointestinal Disorders				
Diarrhea[d]	37.0	3.8	35.1	3.7
Nausea	34.0	1.5	31.3	1.9
Abdominal pain[e]	29.4	2.3	22.0	1.1
Vomiting	24.5	0	19.8	1.5
Dyspepsia	11.3	0.4	8.6	0.7
General Disorders and Administrative Site Conditions				
Edema[f]	18.9	0.4	19.0	1.5
Infections and infestations				
Sepsis[g]	30.2	18.5	25.7	20.1
Upper respiratory tract infections[h]	18.1	1.9	10.1	2.2
Fungal infections[i]	15.1	5.7	9.7	3.0
Herpes infections[j]	14.0	3.0	8.2	1.5
Metabolism and Nutrition Disorders				
Decreased appetite	17.4	4.9	13.4	1.9
Nervous System Disorders				
Headache[k]	27.5	0	19.8	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Epistaxis	15.1	1.1	10.8	0.4

System Organ Class / preferred term	VANFLYTA + Standard Chemotherapy N=265		Placebo + Standard Chemotherapy N=268	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Investigations				
Electrocardiogram QT prolonged[l]	14.0	3.0	4.1	1.1

Standard Chemotherapy = cytarabine (cytosine arabinoside) and anthracycline (daunorubicin or idarubicin)
[a] Including fatalities
[b] Includes neutropenia and neutrophil count decreased.
[c] Includes thrombocytopenia and platelet count decreased.
[d] Diarrhea includes diarrhea and diarrhea hemorrhagic.
[e] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower and gastrointestinal pain.
[f] Edema includes edema peripheral, face edema, edema, fluid overload, generalized edema, peripheral swelling, localized edema and face swelling.
[g] Sepsis includes acinetobacter infection, bacteremia, bacterial sepsis, corynebacterium bacteremia, device related bacteremia, device related sepsis, enterobacter sepsis, enterococcal bacteremia, enterococcal sepsis, escherichia bacteremia, escherichia sepsis, klebsiella bacteremia, klebsiella sepsis, neutropenic sepsis, pseudomonal bacteremia, pulmonary sepsis, sepsis, septic shock, staphylococcal bacteremia, staphylococcal infection, staphylococcal sepsis, stenotrophomonas sepsis, streptococcal sepsis, and streptococcal bacteremia.
[h] Upper respiratory tract infections include upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, tonsillitis, laryngopharyngitis, pharyngitis bacterial, pharyngotonsillitis, viral pharyngitis and acute sinusitis.
[i] Fungal infections include oral candidiasis, bronchopulmonary aspergillosis, fungal infection, vulvovaginal candidiasis, aspergillus infection, lower respiratory tract infection fungal, oral fungal infection, candida infection, fungal skin infection, mucormycosis, oropharyngeal candidiasis, aspergillosis oral, hepatic infection fungal, hepatosplenic candidiasis, onychomycosis, fungemia, systemic candida and systemic mycosis.
[j] Herpes infections include oral herpes, herpes zoster, herpes virus infections, herpes simplex, human herpesvirus 6 infection, genital herpes and herpes dermatitis.
[k] Headache includes headache, tension headache and migraine.
[l] Electrocardiogram QT prolonged includes electrocardiogram QT prolonged and electrocardiogram QT interval abnormal.

Cardiac Disorders

VANFLYTA prolongs the QT interval on ECG. Any grade QT interval prolongation treatment emergent adverse events were reported in 14.0% of VANFLYTA-treated patients. Three percent of patients experienced events of Grade 3 or higher severity. QT prolongation was associated with dose reduction in 10 (3.8%) patients, dose interruption in 7 (2.6%) patients, and discontinuation in 2 (0.8%) patients. QTcF >500 ms occurred in 2.3% of patients based on central review of ECG data. 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 hypokalemia.

8.3. Less Common Clinical Trial Adverse Reactions

Less common adverse reactions reported in <10% of patients treated with VANFLYTA in QuANTUM-First are shown below.

Blood and lymphatic system disorders: pancytopenia

Cardiac disorders: cardiac arrest; ventricular fibrillation

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Table 7: New or Worsening Laboratory Abnormalities (in ≥10% of Subjects with ≥2% Difference for Quizartinib Compared to Placebo) in QuANTUM-First Study (Safety Analysis Set)

Laboratory Abnormality[a]	VANFLYTA + Standard Chemotherapy N=265		Placebo + Standard Chemotherapy N=268	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Lymphocyte count decreased	60.3	57.0	54.5	51.4
Hypokalemia	58.5	21.9	55.6	18.0
Hypoalbuminemia	53.0	1.6	44.9	4.3
Aspartate aminotransferase increased	52.9	5.9	49.2	3.8
Hypophosphatemia	52.2	21.9	48.4	19.0
Alkaline phosphatase increased	51.2	1.6	47.0	1.9
Hypomagnesemia	44.4	2.0	41.6	1.2
Hypocalcemia	32.5	2.4	27.2	1.6
Creatine phosphokinase increased	25.6	2.5	7.0	0.5
Cholesterol high	25.3	1.2	23.1	0

[a] Terms based on laboratory data.
The denominator used to calculate the rate varied from 199 to 260 in VANFLYTA + Chemotherapy and from 187 to 267 in PLACEBO + Chemotherapy based on the number of patients with a baseline value and at least one post-treatment value except for Cholesterol high (CHOL) which is only collected at Screening and end of treatment with 83 as the denominator in VANFLYTA + Chemotherapy and 91 as the denominator in PLACEBO + Chemotherapy.

Table 8: New or Worsened QTcF Prolongation in QuANTUM-First Study (Safety Analysis Set)

QTcF Interval, ms	VANFLYTA + Standard Chemotherapy N=265 %	Placebo + Standard Chemotherapy N=268 %
New >480	7.5	2.2
New >500	2.3	0.7
Increase >60 ms from baseline	10.2	4.9

Note: Based on central assessment of ECG. "New" implies a newly occurring ECG abnormality, which is defined as an abnormal postbaseline ECG finding that is not present at baseline.
ms = millisecond

9. Drug Interactions

9.2. Drug Interactions Overview

Quizartinib and its active metabolite AC886 are primarily metabolized by CYP3A *in vitro*.

Concomitant administration of a strong CYP3A4/5 inhibitor with VANFLYTA requires a dose reduction (see 4.2 Recommended Dose and Dosage Adjustment, Table 4). Strong and moderate CYP3A4 inducers should be avoided (see 9.4 Drug-Drug Interactions, Table 9).

Co-administration of VANFLYTA with other medicinal products that prolong the QT interval may further increase the incidence of QT prolongation (see 9.4 Drug-Drug Interactions, Table 9).

9.3. Drug-Behaviour Interactions

The interaction of VANFLYTA with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

The drugs listed in Table 9 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 9: Established or Potential Drug-Drug Interactions

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
Strong CYP3A4/5 Inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, nefazodone, telithromycin and antiretroviral medications)	CT	Co-administration of ketoconazole (200 mg twice daily for 28 days) with single dose administration of VANFLYTA increased C_{max} and AUC_{inf} to 1.17-fold and 1.94-fold, respectively. At steady state, exposure (C_{max} and AUC_{0-24h}) was estimated to be increased to 1.86-fold and 1.96-fold, respectively	When strong CYP3A4/5 inhibitors cannot be avoided, the dose of VANFLYTA should be reduced as shown in 4.2 Recommended Dose and Dosage Adjustment, Table 4.
Moderate CYP3A4 Inhibitors (e.g., fuconazole)	CT	Co-administration of 200 mg fluconazole twice daily for 28-days did not have a clinically meaningful impact on quizartinib exposure.	No dose modification recommended.
Strong CYP3A4 inducers (e.g., apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin, and certain herbal medicines such as St. John's Wort (also known as *Hypericum perforatum*) or moderate CYP3A4 inducers (e.g., efavirenz, bosentan, etravirine, phenobarbital and primidone)	CT, T	Concomitant use of VANFLYTA with a moderate CYP3A4 inducer reduced the exposure of quizartinib and its active metabolite AC886 compared to the use of VANFLYTA alone in healthy subjects. Quizartinib C_{max} and AUC_{inf} decreased by 45% and 90%, respectively, when co-administered with efavirenz. The C_{max} and AUC_{inf} of AC886 decreased by 68% and 96%, respectively (see 4.2 Recommended Dose and Dosage Adjustment).	Avoid coadministration of VANFLYTA with strong or moderate CYP3A4 inducers. Decreased quizartinib exposure may lead to reduced efficacy.

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
QT Interval Prolonging Medications (e.g., antifungal azoles, ondansetron, granisetron, azithromycin, pentamidine, doxycycline, moxifloxacin, atovaquone, prochlorperazine and tacrolimus)	T	The exposure-response analyses predicted a concentration-dependent QTcF interval median prolongation of 18 and 24 ms [upper bound of 2-side 90% confidence interval (CI): 21 and 27 ms] at the median steady-state C_{max} of quizartinib at the 26.5 mg and 53 mg dose level during maintenance therapy.	Use caution when co-administering drugs that prolong the QT interval with VANFLYTA. See 7 Warnings and Precautions, Cardiovascular.
Gastric Acid Reducing Agents (e.g. lansoprazole)	CT	There were no clinically meaningful changes to quizartinib exposure with coadministration of gastric acid reducing agent (60 mg lansoprazole for 5 days).	No dose modification recommended.
P-glycoprotein (P-gp) Substrates	CT	Co-administration of quizartinib and dabigatran etexilate (a P-gp substrate) increased total and free dabigatran C_{max} to 1.12-fold and 1.13-fold, respectively, and increased total and free dabigatran AUC_{inf} to 1.13-fold and 1.11-fold, respectively.	No dose modification is recommended when P-gp substrates are co-administered with VANFLYTA.
Breast-Cancer Resistant Protein (BCRP) Substrates	T	Quizartinib inhibits BCRP with an estimated *in vitro* IC_{50} of 0.813 µM.	As no clinical data are available, it cannot be excluded that VANFLYTA could inhibit this transporter at the recommended doses.
Uridine Diphosphate Glucuronosyltransferases (UGT) 1A1 Substrates	T	Quizartinib inhibits UGT1A1 with an estimated in vitro K_i of 0.78 µM. Based on a physiologically based pharmacokinetic (PBPK) analysis, quizartinib was predicted to increase the C_{max} and AUC_{inf} of raltegravir (a UGT1A1 substrate) to 1.03-fold.	No dose modification is recommended when UGT1A1 substrates are co-administered with VANFLYTA.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical.

In vitro Studies:

Quizartinib is a substrate of P-gp, but not a substrate of BCRP, OATP1B1, OATP1B3, OCT1, OAT2, MATE1, or MRP2. AC886 is a substrate of BCRP but not a substrate of OATP1B1, OATP1B3, MATE1, or MRP2.

Quizartinib is not an inducer of CYP3A4, CYP1A2, or CYP2B6. Quizartinib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. AC886 is not an inducer of CYP3A4, CYP1A2, or CYP2B6. AC886 is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2C19, or CYP3A4.

9.5. Drug-Food Interactions

VANFLYTA can be administered with or without food (see 10.3 Pharmacokinetics).

9.6. Drug-Herb Interactions

Drug-herb interactions have not been studied. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4 that may decrease quizartinib plasma concentrations and should be avoided.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Quizartinib is a small molecule inhibitor of the FMS-related receptor tyrosine kinase (FLT3). Quizartinib and its major circulating active metabolite AC886 bind to the adenosine triphosphate (ATP) binding pocket of FLT3 with comparable affinity. Quizartinib and AC886 inhibit FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signaling and blocking *FLT3*-ITD-dependent cell proliferation.

10.2. Pharmacodynamics

Cardiac Electrophysiology

The exposure-response analysis of QuANTUM-First predicted a concentration-dependent QTcF interval prolongation of 24.1 ms (upper bound of two-sided 90% CI: 26.6 ms) at the steady-state C_{max} of quizartinib (53 mg) during maintenance therapy.

10.3. Pharmacokinetics

The pharmacokinetics of quizartinib and its active metabolite AC886 were evaluated in healthy adult volunteers (single dose) and in patients with newly diagnosed AML (steady state).

Steady state quizartinib concentrations were achieved at day 15 following once daily dosage in

patients with AML. Quizartinib exhibited dose proportional pharmacokinetics (AUC and C_{max}) in the dose range of 26.5 mg to 79.5 mg in healthy subjects and 17.7 mg to 53 mg in AML patients.

Table 10: Treatment Phase Dependent Quizartinib and Major Metabolite AC886 Pharmacokinetic Parameters in Patients with AML (QuANTUM-First)

Phase/Dose	N	Parameter, Geometric Mean (%CV)[a]		
		AUC_{ss} (ng•h /mL)[b]	$C_{max,ss}$ (ng/mL)[b]	$T_{max,ss}$ (h)[c]
Quizartinib steady state mean				
Induction/35.4 mg	259	2,680 (84.9)	140 (71.2)	2.68 (1.52, 7.30)
Consolidation/35.4 mg	164	3,930 (77.6)	204 (63.5)	2.70 (1.74, 5.95)
Maintenance/26.5 mg	115	5,080 (74.7)	265 (59.7)	2.73 (1.74, 5.95)
Maintenance/53 mg	115	10,200 (74.7)	529 (59.7)	2.73 (1.74, 5.95)
AC886 steady state mean				
Induction/35.4 mg	259	3,590 (51.1)	163 (51.9)	4.59 (1.59, 9.64)
Consolidation/35.4 mg	164	3,800 (45.8)	172 (47.1)	4.62 (2.66, 9.64)
Maintenance/26.5 mg	115	2,890 (46.1)	131 (47.9)	4.77 (2.27, 9.64)
Maintenance/53 mg	115	5,790 (46.1)	262 (47.9)	4.77 (2.27, 9.64)

[a] Generated by Population Pharmacokinetic Model
[b] Reported as geometric mean (%CV)
[c] Reported as median (min, max).

Absorption

The absolute bioavailability of quizartinib from the tablet formulation was 71% (±7%). After oral administration under fasted conditions, time to peak concentration (median T_{max}) of quizartinib and AC886 measured post dose was approximately 4 hours (range 2 to 8 hours) and 5 to 6 hours (range 4 to 120 hours), respectively, in healthy subjects.

Food effect

The extent (AUC_T) and rate (C_{max}) of quizartinib absorption were not significantly affected when VANFLYTA was co-administered with food. The T_{max} was delayed by 2 hours. VANFLYTA can be administered with or without food.

Distribution

The geometric mean (%CV) volume of distribution at steady state (Vss) of quizartinib in healthy subjects was estimated to be 275 L (17%).

In vitro binding of quizartinib and AC886 to human plasma proteins is greater than or equal to 99%.

Quizartinib and AC886 partition into red blood cells with blood-to-plasma ratios ranging from 0.79-1.30 and 1.36-3.19, respectively, in the concentration range of 10 to 1,000 ng/mL studied *in vitro*.

Metabolism

Quizartinib is primarily metabolized by CYP3A4/5 *in vitro* via oxidative pathways which produces the active metabolite AC886, which is then further metabolized by CYP3A4/5.

Elimination

The geometric mean (%CV) total body clearance (CL) of quizartinib in healthy subjects was estimated to be 2.23 (29%) L/hour.

The mean standard deviation (SD) effective half-lives ($t_{1/2}$) for quizartinib and AC886 are 81 hours (±73) and 136 hours (±113), respectively, in patients with newly diagnosed AML.

Following a single radiolabeled dose of quizartinib 53 mg to healthy subjects, 76.3% of the total radioactivity was recovered in feces (4% unchanged) and 1.64% in urine.

Special populations and conditions

- **Pediatrics**

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. No results are currently available from ongoing studies to investigate the pharmacokinetics of quizartinib in pediatric patients.

- **Geriatrics**

No clinically significant differences in quizartinib pharmacokinetics were noted between patients 65 years of age and older and those under 65 years based on a population pharmacokinetic analysis.

- **Sex**

No clinically significant differences in quizartinib pharmacokinetics were noted between male and female patients based on a population pharmacokinetic analysis.

- **Ethnic origin**

No clinically significant differences in quizartinib pharmacokinetics were noted based on the covariate of race (White, Asian, Black or African American) according to population pharmacokinetic analysis.

- **Hepatic Insufficiency**

In two single dose (26.5 mg) phase 1 studies, the pharmacokinetics of quizartinib and AC886 were assessed in subjects with mild hepatic impairment (Child Pugh Class A) or moderate hepatic impairment (Child Pugh Class B or total bilirubin at >1.5 to 3 times ULN and any value for AST) and compared to subjects with normal hepatic function. The exposures (C_{max} and AUC_{inf}) of quizartinib, aggregate quizartinib and AC886 were relatively similar (≤30% difference) across all groups. Population pharmacokinetic analysis including mostly subjects with normal and mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN or total

bilirubin >1 to 1.5 times ULN and any value for AST) showed that hepatic function did not affect quizartinib and AC886 clearance. Therefore, mild and moderate hepatic impairment did not have a clinically meaningful effect on quizartinib and AC886 exposure. No dose adjustment is recommended in patients with mild or moderate hepatic impairment.

Patients with severe hepatic impairment (Child Pugh Class C or total bilirubin >3 times ULN and any value for AST) were not included in the clinical studies, and therefore, VANFLYTA is not recommended for use in these patients.

- **Renal Insufficiency**

A population pharmacokinetic analysis in AML patients with mild to moderate renal impairment (CLcr 30 to 89 mL/min estimated by Cockcroft-Gault) showed that renal function did not affect quizartinib and AC886 clearance. Therefore, mild and moderate renal impairment did not have a clinically meaningful effect on quizartinib and AC886 exposure. No dose adjustment is recommended in patients with mild or moderate renal impairment.

Patients with severe renal impairment (CLcr <30 mL/min) were not included in the clinical trials, and therefore, VANFLYTA is not recommended for use in these patients.

- **Obesity**

No clinically significant differences in quizartinib pharmacokinetics were noted based on body weight (range 37 to 153 kg) according to population pharmacokinetic analysis.

11. Storage, Stability, and Disposal

Store VANFLYTA at room temperature (15°C to 30°C). Keep out of the reach and sight of children.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance: Quizartinib hydrochloride

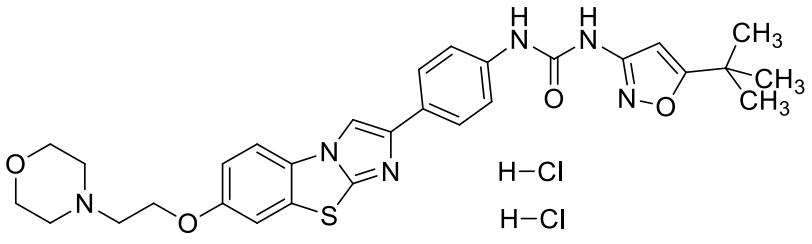
Chemical name: 1-(5-tert-butyl-1,2-oxazol-3-yl)-3-(4-{7-[2-(morpholin-4-yl)ethoxy]imidazo[2,1-b][1,3]benzothiazol-2-yl}phenyl)urea dihydrochloride

Molecular formula and molecular mass: $C_{29}H_{32}N_6O_4S \bullet 2\ HCl$

633.59 (as quizartinib dihydrochloride)

560.67 (as quizartinib free base)

Structural formula:



Physicochemical properties: Quizartinib dihydrochloride is a white to off-white solid with a molecular weight of 633.6 for the salt and 560.7 for the free base. The aqueous solubility of quizartinib dihydrochloride (pKa 4.75 and 3.16) decreases with increasing pH. It is very slightly soluble at pH 1, and practically insoluble or insoluble at pH 2 and higher. Quizartinib dihydrochloride is very slightly soluble in ethanol.

14. Clinical Trials

14.1. Clinical Trials by Indication

Newly diagnosed FLT3-ITD positive acute myeloid leukemia (AML)

Table 11: Summary of Patient Demographics in QuANTUM-First in Patients with Newly Diagnosed *FLT3*-ITD positive AML

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
QuANTUM-First (AC220-A-U302)	Phase 3, randomized, double-blind, placebo-controlled	Dosing and duration: refer to text below Route of administration: oral	n = 539 VANFLYTA arm: n = 268 Placebo arm: n = 271	54.0 (20—75) years VANFLYTA arm: 53.6 (23—75) years Placebo arm: 54.3 (20—75) years	VANFLYTA arm: Male: 124 (46.3%) Female: 144 (53.7%) Placebo arm: Male: 121 (44.6%) Female: 150 (55.4%)

The efficacy and safety of VANFLYTA versus placebo was investigated in a randomized, double-blind, placebo controlled, phase 3 study (QuANTUM-First). The study enrolled 539 adult patients between 20 and 75 years of age who were newly diagnosed with *FLT3*-ITD positive AML. The *FLT3*-ITD status was determined prospectively by a clinical study assay and verified retrospectively using the companion diagnostic LeukoStrat® CDx *FLT3* Mutation Assay. Patients were stratified by age (<60 versus ≥60 years), white blood cell count at diagnosis (<40x10^9/L versus ≥40x10^9/L), and region (North America, Europe versus Asia, other regions). They were randomized 1:1 to receive VANFLYTA 35.4 mg once daily (n=268) or placebo (n=271) for two weeks in each cycle in combination with standard chemotherapy (induction followed by consolidation for responding patients) followed by maintenance monotherapy with VANFLYTA (26.5 mg once daily for two weeks and 53 mg once daily thereafter) or placebo for up to 36 cycles (28 days/cycle).

Patients received up to 2 cycles of induction chemotherapy (either daunorubicin [60 mg/m^2/day IV on days 1, 2 and 3] or idarubicin [12 mg/m^2/day IV on days 1, 2 and 3] with cytarabine [100 mg/m^2/day or 200 mg/m^2/day allowed if institutional or local standard, IV infusion for 7 days]), followed by post remission therapy which consisted of up to 4 cycles of consolidation chemotherapy and/or HSCT. Consolidation chemotherapy consisted of cytarabine 3.0 g/m^2 for patients less than 60 years old and 1.5 g/m^2 for patients greater than

or equal to 60 years old, administered every 12 hours by IV infusion on days 1, 3 and 5. Patients who proceeded to HSCT stopped receiving study treatment 7 days before the start of a conditioning regimen and initiated maintenance therapy after recovery from the HSCT.

The two randomized treatment groups were generally balanced with respect to baseline demographics, disease characteristics and stratification factors (see Table 12).

Table 12: Demographics and Baseline Characteristics in QuANTUM-First Study (Intent-to-Treat Population)

	Quizartinib (N = 268)	Placebo (N = 271)	Total (N = 539)
Age (years)[a]			
Median	56.0	56.0	56.0
Age, n (%)			
<60 years	161 (60.1)	162 (59.8)	323 (59.9)
≥60 to <65 years	37 (13.8)	44 (16.2)	81 (15.0)
≥65 to 75 years	70 (26.1)	65 (24.0)	135 (25.0)
Race, n (%)			
Asian	80 (29.9)	78 (28.8)	158 (29.3)
Black	2 (0.7)	5 (1.8)	7 (1.3)
White	159 (59.3)	163 (60.1)	322 (59.7)
Other races	27 (10.1)	25 (9.2%)	52 (9.6%)
ECOG, n (%)			
0	87 (32.5)	98 (36.2)	185 (34.3)
1	134 (50.0)	136 (50.2)	270 (50.1)
2	47 (17.5)	36 (13.3)	83 (15.4)
WHO classification, n (%)			
Nucleophosmin (NPM1) mutation	142 (53.0)	140 (51.7)	282 (52.3)
Cytogenetic Risk Classification, n (%)			
Favorable	14 (5.2)	19 (7.0)	33 (6.1)
Intermediate	197 (73.5)	193 (71.2)	390 (72.4)
Unfavorable	19 (7.1)	27 (10.0)	46 (8.5)
Unknown	38 (14.2)	31 (11.4)	69 (12.8)

	Quizartinib (N = 268)	Placebo (N = 271)	Total (N = 539)
***FLT3* ITD VAF (*FLT3* ITD/total FLT3) by central laboratory testing, n (%)**			
≥3 to ≤25%	94 (35.1)	98 (36.2)	192 (35.6)
>25% to ≤50%	143 (53.4)	138 (50.9)	281 (52.1)
>50%	30 (11.2)	35 (12.9)	65 (12.1)
WBC count at diagnosis of AML, n (%)			
$<40 \times 10^9$/L	135 (50.4)	137 (50.6)	272 (50.5)
$\geq 40 \times 10^9$/L	133 (49.6)	134 (49.4)	267 (49.5)

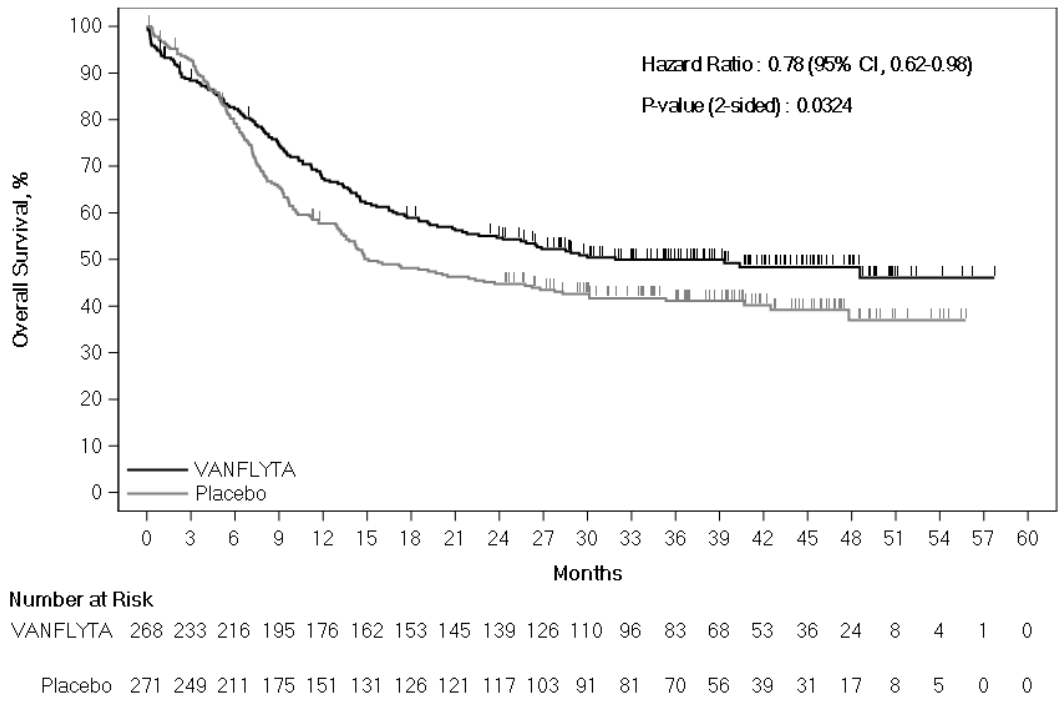
AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; *FLT3* = FMS like tyrosine kinase 3; ITD = internal tandem duplications; NPM1 = nucleophosmin 1; VAF = variant allelic frequency; WBC = white blood cells; WHO = World Health Organization.
The baseline value is defined as the last non missing value before initial administration of study drug.
[a] Age in years is calculated using the birth date and informed consent date.

Study Results

The primary efficacy measure was overall survival (OS) defined as the time from randomization until death from any cause. The median follow-up time of the study was 39.2 months.

The study demonstrated a statistically significant improvement in overall survival with a 22.4% risk reduction of death for VANFLYTA versus placebo (Figure 1).

Figure 1: Kaplan-Meier Curve for Overall Survival in QuANTUM-First



Complete remission (CR) was measured from the date of first CR to the date of relapse or death from any cause. The CR rate in the VANFLYTA arm was 54.9% (95% CI: 48.7, 60.9) with a median duration of CR of 38.6 months (95% CI: 21.9, NE) and the CR rate in the placebo arm was 55.4% (95% CI: 49.2, 61.4) with a median duration of CR of 12.4 months (95% CI: 8.8, 22.7).

In an exploratory subgroup analysis of the 89 (43%) patients who received maintenance therapy with VANFLYTA or placebo following consolidation chemotherapy without HSCT, the OS HR was 0.40 (95% CI: 0.19-0.84). Of 119 (57%) patients who received maintenance therapy with VANFLYTA or placebo following HSCT, the OS HR was 1.62 (95% CI: 0.62, 4.22).

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General toxicology

In repeat dose toxicity studies conducted in rats, dogs and monkeys, principal organs of toxicity were hematopoietic and lymphoid organs. Additional toxicities were observed in the liver, kidneys and reproductive organs.

In 13-week repeat-dose studies, quizartinib was administered orally at doses of 1, 3 and 10 mg/kg/day in the rat, 1, 5 and 15 mg/kg/day in the dog and 3, 6 and 12 mg/kg/day in the monkey, followed by a 4-week recovery period.

Hematopoietic organ toxicities were observed in all species and manifested in decreased red blood cells (RBC) and RBC parameters, decreased reticulocytes and white blood cells (WBC), correlating with hematopoietic hypocellularity in the bone marrow and lymphoid atrophy/necrosis in the thymus; in the spleen, extramedullary hematopoiesis and pigment deposition (rats, dogs) and lymphoid atrophy (monkeys) were also observed. These changes were mostly reversed at the end of the recovery period. Liver toxicity included increased aminotransferases (mostly reversed after recovery) in all species, hepatocellular vacuolation and necrosis (dogs, monkeys), birefringent crystal deposition, fibrosis, inflammation, reactive sinusoidal lining cells and bile duct hyperplasia in dogs; these changes were partially reversed after the recovery period. Kidney toxicity included tubular vacuolation and birefringent crystal deposition (rats) and tubular basophilia (rats, dogs) that were partially reversed following recovery. Clinical signs including reduced appetite/body weight, hunched posture, dehydration and uncoordination were observed in monkeys at the high dose. In dogs and monkeys, these changes were observed at exposures lower than the recommended human dose (RHD) based on AUC, while in the rat they were observed at exposures higher than the RHD. The no observed adverse effect levels (NOAEL) were considered to be 3 mg/kg/day in the rat, 5 mg/kg/day in the dog and 3 mg/kg/day in the monkey, corresponding to 1.19, 0.39 and 0.07 times the RHD based on AUC for rats, dogs and monkeys, respectively.

In vitro and Animal Safety Pharmacology Studies

In cardiovascular studies conducted in cynomolgus monkeys, quizartinib resulted in QT prolongation at doses approximately 2 times the RHD of 53 mg/day based on C_{max}. In *in vitro* studies, quizartinib primarily inhibited the slowly activating component of delayed rectifier potassium currents (IKs).

Genotoxicity

In genotoxicity studies, quizartinib was mutagenic in a bacterial reverse mutation assay, but not in a mammalian cell mutation assay (mouse lymphoma thymidine kinase) or in an *in vivo* transgenic rodent mutation assay. Quizartinib was not clastogenic in an *in vitro* chromosome aberration assay in peripheral blood lymphocytes and was not clastogenic or aneugenic in the rat bone marrow micronucleus assay after a single dose, but produced equivocal results following 28 days administration.

Carcinogenicity

No carcinogenicity studies were conducted with quizartinib.

Reproductive and developmental toxicology

In embryo-fetal reproductive toxicity studies, pregnant rats were administered oral doses of quizartinib during the period of organogenesis. Fetotoxicity (lower fetal weights, effects on skeletal ossification) and teratogenicity (fetal abnormalities including edema) were observed at 6 mg/kg/day (approximately 3 times the RHD of 53 mg/day based on AUC). At doses >10 mg/kg/day, embryo-fetal lethality and increased post-implantation loss were observed. Maternal toxicity was evident at >10 mg/kg/day by decreased body weight gains and lower food consumption and at 20 mg/kg/day by adverse clinical signs. Based on maternal toxicity and fetal effects, the NOAEL was considered to be 6 and 2 mg/kg/day, corresponding to approximately 2.75 and 0.43 times the RHD of 53 mg/day based on AUC, respectively.

Fertility studies in animals have not been conducted with quizartinib. However, adverse findings in male and female reproductive systems were observed in repeat dose toxicity studies in rats and monkeys. In female rats, ovarian cysts and vaginal mucosal modifications were observed at 10 mg/kg/day (approximately 8.41 times the RHD of 53 mg/day based on AUC). Findings in female monkeys included atrophy of the uterus, ovary, and vagina observed at ≥6 mg/kg/day (approximately 0.24 times the RHD). In male rats, decreased testis weight, testicular seminiferous tubular degeneration and failure of sperm release were observed at 10 mg/kg/day (approximately 6.41 times the RHD). Findings in male monkeys included germ cell depletion in the testes observed at ≥6 mg/kg/day (approximately 0.40 times the RHD). After a four-week recovery period, all these findings except the vaginal mucosal modifications in the female rats were reversed.

Special Toxicology

In local tolerance studies in rabbits, quizartinib was considered a mild irritant of the ocular tissue and a slight irritant of the skin. In *in vitro* studies on 3T3 cells, quizartinib was found to have low potential for phototoxicity.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrVANFLYTA®

Quizartinib tablets

This patient medication information is written for the person who will be taking **VANFLYTA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **VANFLYTA**, talk to a healthcare professional.

Serious warnings and precautions box

VANFLYTA may cause serious side effects, including:

- Changes in the electrical activity of your heart called **prolonged QT interval**.
- Heart rhythm problems called **torsades de pointes** and **ventricular fibrillation**.
- **Cardiac arrest**, which means your heart stops beating.
- **Sudden death**.

Before and during treatment with VANFLYTA:

Your healthcare professional will check the electrical activity of your heart with a test called an electrocardiogram (ECG). They will also do blood tests to check your potassium and magnesium levels. If you get QT prolongation while taking VANFLYTA, your healthcare professional might reduce your dose or stop treatment. They may also reduce your dose if you are taking certain other medicines that interact with VANFLYTA.

Stop taking VANFLYTA and get immediate medical help if you have any symptoms of **ventricular fibrillation or cardiac arrest.** Talk to your healthcare professional if you get any symptoms of **prolonged QT interval. See "Serious side effects and what to do about them"** for symptoms. Also, you will receive a **Patient Card** on these serious side effects from your healthcare professional. Refer to it for more information, carry it with you and show it to all of your healthcare professionals.

What VANFLYTA is used for:

- VANFLYTA is used to treat a cancer of the blood and bone marrow called acute myeloid leukemia (AML).

- It is used in adults with newly diagnosed AML who have a genetic mutation called "*FLT3*-ITD". Your healthcare professional will test your cancer cells to look for *FLT3*-ITD mutations to make sure that VANFLYTA is right for you.
- At the beginning of treatment, VANFLYTA is given in combination with certain chemotherapy medicines. Treatment with VANFLYTA alone then continues as maintenance therapy.

VANFLYTA is not approved for use in children and adolescents less than 18 years of age.

How VANFLYTA works:

VANFLYTA works by blocking the action of proteins called "kinases" in cancer cells. This slows down or stops cancer cells from dividing and growing.

The ingredients in VANFLYTA are:

Medicinal ingredient(s): quizartinib, as quizartinib hydrochloride

Non-medicinal ingredients:

Ferric oxide yellow (26.5 mg only), hypromellose, hydroxypropyl betadex, magnesium stearate, microcrystalline cellulose, magnesium stearate, talc, titanium dioxide, triacetin.

VANFLYTA comes in the following dosage form:

Tablets: 17.7 mg and 26.5 mg quizartinib (as quizartinib hydrochloride).

Do not use VANFLYTA if:

- you were born with a heart rhythm problem called "long QT syndrome" which causes irregular heartbeats.
- you have had heart rhythm problems called ventricular arrhythmias or torsades de pointes in the past.
- you have very low potassium or very low magnesium levels in your blood.
- you are allergic to quizartinib or to any of the other ingredients in VANFLYTA (see 'The ingredients in VANFLYTA are').

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VANFLYTA. Talk about any health conditions or problems you may have, including if you:

- have ever had any heart problems including heart rhythm problems called arrhythmias.
- have ever had an abnormal result from an electrocardiogram (ECG).

- have kidney problems.
- have liver problems.

Other warnings you should know about:

Testing before treatment:

Before you start treatment, your healthcare professional will perform a test to make sure VANFLYTA is the right medicine for you. They will also check your heart with an electrocardiogram (ECG) and will do a blood test to check the potassium and magnesium levels in your blood.

Testing during treatment:

Your healthcare professional will perform regular blood tests during treatment with VANFLYTA to check your blood cells and your potassium and magnesium levels. Your healthcare professional will also regularly check your heart with an ECG while you are taking VANFLYTA.

Use with medicines that prolong the QT interval

Taking VANFLYTA with other medicines that also prolong the QT interval may further increase your chance of getting prolonged QT interval. These medicines include: antifungal azoles (examples include itraconazole, ketoconazole, posaconazole, and voriconazole), ondansetron, granisetron, azithromycin, pentamidine, doxycycline, moxifloxacin, atovaquone, prochlorperazine and tacrolimus. Tell your healthcare professional if you are taking any of these medicines. Your healthcare professional will check your heart more often with an ECG while you are taking VANFLYTA and these medicines.

Pregnancy and birth control

Female patients:

Tell your healthcare professional before taking VANFLYTA if you are pregnant, think you may be pregnant or are planning to become pregnant. You must not take VANFLYTA if you are pregnant. This is because it can harm your unborn baby. If you are able to get pregnant, your healthcare professional will give you a test before you start treatment to make sure you are not pregnant. You must also use effective birth control while you are taking VANFLYTA. You must use it while you are taking VANFLYTA and for at least 7 months after you stop taking it. Talk to your healthcare professional about the best birth control for you. If you do become pregnant while taking VANFLYTA, tell your healthcare professional right away.

Male patients:

If you have a female partner that can get pregnant, you must use effective birth control while taking VANFLYTA. You must continue using this birth control for at least 4 months after you stop taking it.

Breast-feeding:

You must not breastfeed while taking VANFLYTA and for at least 5 weeks after you stop taking it. This is because VANFLYTA might pass into your breast milk and harm your baby.

Fertility:

VANFLYTA may reduce fertility in female and male patients. This means it may be more difficult for you to have a baby in the future. Talk to your healthcare professional if you have questions about this.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VANFLYTA:

- certain medicines to treat infections – such as azithromycin, clarithromycin, doxycycline, moxifloxacin, telithromycin, pentamidine or atovaquone;
- certain medicines used to treat fungal infections – such as ketoconazole, itraconazole, posaconazole or voriconazole;
- certain medicines to prevent and treat nausea and vomiting – such as graniesetron, ondansetron or prochloperazine;
- tacrolimus, a medicine used to prevent and treat graft-versus host disease after stem cell transplant;
- certain medicines used to treat HIV – such as ritonavir, efavirenz or etravirine;
- certain medicines used to treat tuberculosis – such as rifampicin;
- certain medicines used to treat seizures or epilepsy – such as carbamazepine, primidone, phenobarbital or phenytoin;
- bosentan, a medicine used to treat high blood pressure in the lungs (pulmonary arterial hypertension);
- St. John's wort (*Hypericum perforatum*), an herbal product used for anxiety and mild depression;
- nefazodone, a medicine used to treat major depression;
- certain medicines to treat prostatic cancer – such as apalutamide and enzalutamide;
- mitotane, a medicine used for the treatment of symptoms of tumours of the adrenal glands.

How to take VANFLYTA:

- Always take VANFLYTA exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- VANFLYTA will be first prescribed to you by a healthcare professional with experience in anticancer medicines.
- You can take VANFLYTA with or without food.

- Swallow tablets whole with water. Do not cut, crush, or chew the tablets.
- Take VANFLYTA at about the same time each day.
- Your healthcare professional will tell you exactly how much VANFLYTA to take and for how long to take it.
- If you vomit after you take this medicine, do not take any more tablets that day. Take your next dose at the usual scheduled time.

Usual dose:

- Usually, you will start by taking 35.4 mg (two 17.7 mg tablets) once a day for 2 weeks during each cycle of chemotherapy. Your healthcare professional may start you on a lower dose of one 17.7 mg tablet once a day if you are taking certain other medicines.
- After your chemotherapy is completed, your healthcare professional may change your dose to one 26.5 mg tablet once a day for 2 weeks and then increase your dose to 53 mg (two 26.5 mg tablets) once a day going forward depending on how you respond to VANFLYTA.
- The maximum recommended dose is 53 mg once a day.
- Your healthcare professional may temporarily stop your treatment, permanently stop your treatment or change your dose based on blood tests, side effects or because of other medicines you may be taking.
- Your healthcare professional will stop your treatment with VANFLYTA if you are having a stem cell transplant. Your healthcare professional will tell you when to stop taking your medicine and when to restart it.
- Continue taking VANFLYTA for as long as your healthcare professional tells you. Your healthcare professional will regularly monitor your condition.

Overdose:

If you accidentally take more tablets than you should, or if someone else accidentally takes your medicine, talk to a healthcare professional straightaway or go to a hospital and take this patient medication information with you. Medical treatment may be necessary.

If you think you, or a person you are caring for, have taken too much VANFLYTA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget to take VANFLYTA, take it as soon as possible on the same day. Take your next dose at your usual time on the next day. Never take two doses on the same day to make up for a missed dose.

Possible side effects from using VANFLYTA:

These are not all the possible side effects you may have when taking VANFLYTA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Nausea
- Abdominal pain
- Headache
- Decreased appetite
- Nosebleeds
- Indigestion

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
Very common			
Prolonged QT interval (changes in the electrical activity of your heart that lead to abnormal heart rhythm): feeling dizzy, lightheaded, or faint; irregular or fast heartbeat		x	
Hypokalemia (low level of potassium in the blood): muscle weakness, muscle spasms, cramping, constipation, fatigue, irregular heartbeats, tingling or numbness		x	
Abnormal liver enzyme blood test results: dark urine, fatigue, loss of appetite, nausea or vomiting, sleepiness, bleeding or bruising, yellowing of the skin or eyes, pain		x	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
on the upper right side of the stomach area			
Hypomagnesemia (low level of magnesium in the blood): abnormal eye movements, fatigue, irregular heartbeats, muscle spasms or cramps, muscle weakness, numbness		x	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, small purple dots (tiny bleeds) on your skin, fatigue, and weakness		x	
Anemia (low red blood cells): being short of breath, feeling very tired or cold, having pale skin, fast heartbeat, loss of energy, or weakness		x	
Neutropenia (low white blood cells): fever or infection, fatigue, aches and pains, flu-like symptoms		x	
Diarrhea		x	
Vomiting		x	
Edema (excess fluid build-up inside the body): swelling of the face, arms, and legs		x	
Upper respiratory tract infections: cough, sore throat, stuffy or runny nose, sneezing	x		
Fungal infections: **Oral thrush**: creamy white, sore patches in your mouth or on your tongue, aching muscles with high temperature, sore throat, and swollen glands		x	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
Lung infections: fever, cough, chest pain, shortness of breath, coughing up blood **Brain infections:** lethargy, seizures, slurred speech, partial paralysis Skin blisters or ulcers Nausea, vomiting, diarrhea, bloody diarrhea			
Herpes virus infections: blisters on lips, mouth, genitals, painful rash of blister-like sores, usually on one side of the body, often on the face or torso, fever, headache, chills		x	
Bacteremia (bacteria present in the blood) or **Sepsis** (serious response to blood infection): chills, fever, shaking or shivering, fast heart rate, low blood pressure, abdominal pain, nausea, vomiting, diarrhea, rapid breathing		x	
Common			
Pancytopenia (decrease in the number of all types of blood cells): **See symptoms of Anemia, Neutropenia and Thrombocytopenia in this table.**		x	
Uncommon			
Cardiac arrest (heart stops beating): sudden collapse, loss of consciousness, loss of heartbeat, unresponsiveness to touch or sound, not breathing normally or at all or making gasping sounds			x
Ventricular fibrillation (serious heart rhythm problem): sudden collapse, loss of consciousness, fainting, dizziness, loss of heartbeat, unresponsive to touch			x

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
or sound, shortness of breath, not breathing normally or at all, or making gasping sounds			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store VANFLYTA at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about VANFLYTA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.daiichi-sankyo.ca; or by calling 1-866-791-9292.

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