ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 17.7 mg film-coated tablets
VANFLYTA 26.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VANFLYTA 17.7 mg film-coated tablets

Each film-coated tablet contains 17.7 mg quizartinib (as dihydrochloride).

VANFLYTA 26.5 mg film-coated tablets

Each film-coated tablet contains 26.5 mg quizartinib (as dihydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

VANFLYTA 17.7 mg film-coated tablets

White, round-shaped film-coated tablets, 8.9 mm in diameter and debossed with 'DSC 511' on one side.

VANFLYTA 26.5 mg film-coated tablets

Yellow, round-shaped film-coated tablets, 10.2 mm in diameter and debossed with 'DSC 512' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive.

4.2 Posology and method of administration

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

Before taking VANFLYTA, AML patients must have confirmation of FLT3-ITD positive AML using a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If a CE-marked IVD is not available, confirmation of FLT3-ITD positive AML should be assessed by an alternate validated test.

ECGs should be performed, and electrolyte abnormalities should be corrected prior to initiation of treatment (see section 4.4).

Posology

VANFLYTA should be administered in combination with standard chemotherapy at a dose of 35.4 mg (2 × 17.7 mg) once daily for two weeks in each cycle of induction. For patients who achieve complete remission (CR) or complete remission with incomplete haematologic recovery (CRi), VANFLYTA should be administered at 35.4 mg once daily for two weeks in each cycle of consolidation chemotherapy followed by VANFLYTA single-agent maintenance therapy initiated at 26.5 mg once daily. After two weeks the maintenance dose should be increased to 53 mg (2 × 26.5 mg) once daily if the QT interval corrected by Fridericia's formula (QTcF) is ≤ 450 ms (see Table 2 and section 4.4). Single-agent maintenance therapy may be continued for up to 36 cycles.

For additional dosing information see Tables 1 to 3.

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.

Haematopoietic stem cell transplantation
For patients who proceed to haematopoietic stem cell transplantation (HSCT), VANFLYTA should be stopped 7 days before the start of a conditioning regimen. It 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 haematologic recovery and with ≤ 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
VANFLYTA should be initiated only if QTcF is ≤ 450 ms (see section 4.4).

For recommended dose modifications due to adverse reactions, see Table 2. For dose adjustments due to adverse reactions and/or concomitant use with strong CYP3A inhibitors, see Table 3.

Table 2: Recommended dose modifications for adverse reactions

Adverse reaction	**Recommended action**
QTcF 450-480 ms (Grade 1)	• Continue VANFLYTA dose.
QTcF 481-500 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 < 450 ms. Monitor the patient closely for QT prolongation for the first cycle at the increased dose.

QTcF ≥ 501 ms (Grade 3)	• 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 (Grade 3)	• 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).
Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of life-threatening arrhythmia (Grade 4)	• Permanently discontinue VANFLYTA.
Grade 3 or 4 non-haematologic adverse reactions	• Interrupt VANFLYTA. • Resume treatment at the previous dose if adverse reaction improves to ≤ Grade 1. • Resume treatment at a reduced dose (see Table 3) if adverse reaction improves to < Grade 3. • Permanently 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).

Dose adjustments for adverse reactions and/or concomitant use with strong CYP3A inhibitors

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

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 but take the next dose the following day at the usual time.

Special populations

Elderly
No dose adjustment is required in the elderly.

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), as safety and efficacy have not been established in this population.

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 (CLcr < 30 mL/min, estimated by Cockcroft-Gault), as safety and efficacy have not been established in this population.

Paediatric population
The safety and efficacy of VANFLYTA in children and adolescents less than 18 years of age have not been established (see section 5.1). No data are available.

Method of administration

VANFLYTA is for oral use.
The tablets should be taken at approximately the same time each day with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Congenital long QT syndrome (see section 4.4).
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

QT interval prolongation

Quizartinib is associated with QT interval prolongation (see section 4.8). QT interval prolongation may increase the risk of ventricular arrhythmias or torsade de pointes. Patients with congenital long QT syndrome and/or a previous history of torsade de pointes were excluded from the quizartinib development programme. 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. These include 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. Electrolytes should be maintained in the normal range (see section 4.2).

Do not start treatment with VANFLYTA if the QTcF interval is greater than 450 ms.

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).

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

ECG monitoring of the QT interval should be performed more frequently in patients who are at significant risk of developing QT interval prolongation and torsade de pointes.

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 with QT interval prolonging medicinal products
Patients should be monitored more frequently with ECG if co-administration of VANFLYTA with medicinal products known to prolong the QT interval is required (see section 4.5).

Co-administration with strong CYP3A inhibitors
The dose of VANFLYTA should be reduced when used concomitantly with strong CYP3A inhibitors as they may increase quizartinib exposure (see sections 4.2 and 4.5).

Infections in elderly patients

Fatal infections have occurred more frequently with quizartinib in elderly patients (i.e., older than 65 years), compared to younger patients especially in the early treatment period. Patients older than 65 years of age should be closely monitored for the occurrence of severe infections during induction.

Women of childbearing potential/Contraception in males and females

Based on findings in animals, quizartinib may cause embryo-foetal harm when administered to a pregnant woman. Women of childbearing potential should undergo pregnancy testing within 7 days before starting treatment with VANFLYTA. Women of childbearing potential should use effective contraception during treatment with VANFLYTA and for at least 7 months after the last dose. Male patients with female partners of childbearing potential should use effective contraception during treatment with VANFLYTA and for at least 4 months after the last dose (see section 4.6).

Patient card

The prescriber must discuss the risks of VANFLYTA therapy with the patient. The patient will be provided with the patient card with each prescription (included in the medicinal product pack).

4.5 Interaction with other medicinal products and other forms of interaction

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

Effect of other medicinal products on VANFLYTA

Strong CYP3A/P-glycoprotein (P-gp) inhibitors
Co-administration of ketoconazole (200 mg twice daily for 28 days), a strong CYP3A/P-gp inhibitor, with a single dose of VANFLYTA increased quizartinib maximum plasma concentration (C_{max}) and area under the curve (AUC_{inf}) by 1.17-fold and 1.94-fold, respectively, and decreased AC886 C_{max} and AUC_{inf} by 2.5-fold and 1.18-fold, respectively, compared to VANFLYTA alone. At steady state, quizartinib exposure (C_{max} and AUC_{0-24h}) was estimated to be increased by 1.86-fold and 1.96-fold, respectively, and AC886 exposure (C_{max} and AUC_{0-24h}) decreased by 1.22-fold and 1.17-fold, respectively. Increased quizartinib exposure may increase the risk of toxicity.

The dose of VANFLYTA should be reduced as shown in the table below if concomitant use with strong CYP3A inhibitors cannot be avoided. For more details regarding dose adjustments, see Table 3 in section 4.2.

Full dose	Dose reductions for concomitant use with strong CYP3A inhibitors
26.5 mg	17.7 mg
35.4 mg	
53 mg	26.5 mg

Examples of strong CYP3A/P-gp inhibitors include itraconazole, posaconazole, voriconazole, clarithromycin, nefazodone, telithromycin and antiretroviral medicinal products (Certain medicines used to treat HIV may either increase the risk of side effects (e.g., ritonavir) or reduce the effectiveness (e.g., efavirenz or etravirine) of VANFLYTA).

Moderate CYP3A inhibitors
Co-administration of fluconazole (200 mg twice daily for 28 days), a moderate CYP3A inhibitor, with a single dose of VANFLYTA increased quizartinib and AC886 C_{max} by 1.11-fold and 1.02-fold, respectively, and AUC_{inf} by 1.20-fold and 1.14-fold, respectively. This change was not considered clinically relevant. No dose modification is recommended.

Strong or moderate CYP3A inducers
Co-administration of efavirenz (lead-in treatment at 600 mg once daily for 14 days), a moderate CYP3A inducer, with a single dose of VANFLYTA decreased quizartinib C_{max} and AUC_{inf} by approximately 1.18-fold and 9.7-fold, respectively, compared to VANFLYTA alone. The C_{max} and AUC_{inf} of AC886 decreased by approximately 3.1-fold and 26-fold, respectively (see section 5.2).

Decreased quizartinib exposure may lead to reduced efficacy. Co-administration of VANFLYTA with strong or moderate CYP3A inducers should be avoided.

Examples of strong CYP3A4 inducers include apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin and certain herbal medicinal products such as St. John's Wort (also known as *Hypericum perforatum*). Examples of moderate CYP3A4 inducers include efavirenz, bosentan, etravirine, phenobarbital and primidone.

QT interval prolonging medicinal products
Co-administration of VANFLYTA with other medicinal products that prolong the QT interval may further increase the incidence of QT prolongation. Examples of QT prolonging medicinal products include but are not limited to antifungal azoles, ondansetron, granisetron, azithromycin, pentamidine, doxycycline, moxifloxacin, atovaquone, prochlorperazine and tacrolimus. Caution should be used when co-administering medicinal products that prolong the QT interval with VANFLYTA (see section 4.4).

Gastric acid reducing agents
Proton pump inhibitor lansoprazole decreased quizartinib C_{max} by 1.16-fold and AUC_{inf} by 1.05-fold. This decrease in quizartinib absorption was not considered clinically relevant. No dose modification is recommended.

Effect of VANFLYTA on other medicinal products

P-glycoprotein (P-gp) substrates
Co-administration of quizartinib and dabigatran etexilate (a P-gp substrate) increased total and free dabigatran C_{max} by 1.12-fold and 1.13-fold, respectively, and increased total and free dabigatran AUC_{inf} by 1.13-fold and 1.11-fold, respectively (see section 5.2). Quizartinib is a weak P-gp inhibitor, and no dose modification is recommended when P-gp substrates are co-administered with VANFLYTA.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should undergo pregnancy testing within 7 days before starting treatment with VANFLYTA.

Quizartinib may cause embryo-foetal harm when administered to pregnant women (see section 5.3); therefore, women of childbearing potential should use effective contraception during treatment with VANFLYTA and for at least 7 months after the last dose.

Male patients with female partners of childbearing potential should use effective contraception during treatment with VANFLYTA and for at least 4 months after the last dose.

Pregnancy

There are no data on the use of quizartinib in pregnant women. Based on findings in animals, quizartinib may cause embryo-foetal toxicity when administered to pregnant women (see section 5.3).

VANFLYTA should not be used during pregnancy and in women of childbearing potential not using contraception, unless the clinical condition of the woman requires treatment. Pregnant women should be advised of the potential risk to the foetus.

Breast-feeding

It is unknown whether quizartinib or its active metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Because of the potential for serious adverse reactions in breast-fed children, women must not breast-feed during treatment with VANFLYTA and for at least 5 weeks after the last dose (see section 4.3).

Fertility

There are no human data on the effect of quizartinib on fertility. Based on findings in animals, female and male fertility may be impaired during treatment with VANFLYTA (see section 5.3).

4.7 Effects on ability to drive and use machines

VANFLYTA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were increased alanine aminotransferase (58.9%), decreased platelet count (40.0%), decreased haemoglobin (37.4%), diarrhoea (37.0%), nausea (34.0%), abdominal pain (29.4%), headache (27.5%), vomiting (24.5%) and decreased neutrophil count (21.9%).

The most common Grade 3 or 4 adverse reactions were decreased platelet count (40%), decreased haemoglobin (35.5%), decreased neutrophil count (21.5%), increased alanine aminotransferase (12.1%), bacteraemia (7.2%) and fungal infections (5.7%). The most common serious adverse reactions in the VANFLYTA arm were neutropenia (3.0%), fungal infections (2.3%) and herpes infections (2.3%). Adverse reactions with fatal outcome were fungal infections (0.8%) and cardiac arrest (0.4%).

The most common adverse reactions associated with dose interruption of VANFLYTA were neutropenia (10.6%), thrombocytopenia (4.5%) and prolonged electrocardiogram QT interval (2.6%).

The most common adverse reactions associated with dose reduction were neutropenia (9.1%), thrombocytopenia (4.5%) and prolonged electrocardiogram QT interval (3.8%).

The most common adverse reaction associated with permanent discontinuation of VANFLYTA was thrombocytopenia (1.1%).

Tabulated list of adverse reactions

The safety of VANFLYTA was investigated in QuANTUM-First, a randomised, double-blind, placebo-controlled study in adult patients with newly diagnosed FLT3-ITD positive AML.

Adverse reactions are listed according to MedDRA System Organ Class (SOC). Within each SOC, the adverse reactions are ranked by frequency with the most frequent reactions first, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse reactions

Adverse reaction	All grades %	Grade 3 or 4 %	Frequency category (All grades)
Infections and infestations			
Upper respiratory tract infections[a]	18.1	1.9	Very common
Fungal infections[b]	15.1	5.7	Very common
Herpes infections[c]	14.0	3.0	Very common
Bacteraemia[d]	11.3	7.2	Very common
Blood and lymphatic system disorders			
Thrombocytopenia[e]	40.0	40.0	Very common
Anaemia[e]	37.4	35.5	Very common
Neutropenia[e]	21.9	21.5	Very common
Pancytopenia	2.6	2.3	Common
Metabolism and nutrition disorders			
Decreased appetite	17.4	4.9	Very common
Nervous system disorders			
Headache[f]	27.5	0	Very common
Cardiac disorders			
Cardiac arrest[g]	0.8	0.4	Uncommon
Ventricular fibrillation[g]	0.4	0.4	Uncommon
Respiratory, thoracic and mediastinal disorders			
Epistaxis	15.1	1.1	Very common
Gastrointestinal disorders			
Diarrhoea[h]	37.0	3.8	Very common
Nausea	34.0	1.5	Very common
Abdominal pain[i]	29.4	2.3	Very common
Vomiting	24.5	0	Very common
Dyspepsia	11.3	0.4	Very common
Hepatobiliary disorders			
ALT increased[e]	58.9	12.1	Very common
General disorders and administration site conditions			
Oedema[j]	18.9	0.4	Very common
Investigations			
Prolonged electrocardiogram QT[k]	14.0	3.0	Very common

Standard chemotherapy = cytarabine (cytosine arabinoside) and anthracycline (daunorubicin or idarubicin).

[a] Upper respiratory tract infections include upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, tonsillitis, laryngopharyngitis, pharyngitis bacterial, pharyngotonsillitis, viral pharyngitis and acute sinusitis.

[b] 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.
[c] Herpes infections include oral herpes, herpes zoster, herpes virus infections, herpes simplex, human herpesvirus 6 infection, genital herpes and herpes dermatitis.
[d] Bacteraemia includes bacteraemia, Klebsiella bacteraemia, Staphylococcal bacteraemia, Enterococcal bacteraemia, Streptococcal bacteraemia, device-related bacteraemia, Escherichia bacteraemia, Corynebacterium bacteraemia and Pseudomonal bacteraemia.
[e] Terms based on laboratory data.
[f] Headache includes headache, tension headache and migraine.
[g] One subject experienced two events (ventricular fibrillation and cardiac arrest).
[h] Diarrhoea includes diarrhoea and diarrhoea haemorrhagic.
[i] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower and gastrointestinal pain.
[j] Oedema includes oedema peripheral, face oedema, oedema, fluid overload, generalised oedema, peripheral swelling, localised oedema and face swelling.
[k] Electrocardiogram QT prolonged includes electrocardiogram QT prolonged and electrocardiogram QT interval abnormal.

Description of selected adverse reactions

Cardiac disorders
Quizartinib prolongs the QT interval on ECG. Any grade QT interval prolongation treatment-emergent adverse reactions were reported in 14.0% of VANFLYTA-treated patients and 3.0% of patients experienced reactions 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 hypokalaemia. Electrocardiograms, monitoring and correction of hypokalaemia and hypomagnesemia should be performed prior to and during treatment with VANFLYTA. For dose modification for patients with QT interval prolongation, see section 4.2.

Other special populations

Elderly
Fatal infections have occurred more frequently with quizartinib in elderly patients (i.e., older than 65 years), compared to younger patients (13% vs. 5.7%), especially in the early treatment period.

Patients older than 65 years of age should be closely monitored for the occurrence of severe infections during induction.

Reporting of suspected adverse reactions

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 national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for overdoses of VANFLYTA. For a substantial overdose, supportive measures should be provided as necessary, with interruption of treatment, evaluation of haematology and ECG monitoring as well as attention to serum electrolytes and concomitant medicinal products that may predispose patients to QT interval prolongation and/or torsade de pointes. Patients should be managed with symptomatic and supportive care (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX11

Mechanism of action

Quizartinib is an inhibitor of the receptor tyrosine kinase FLT3. Quizartinib and its major metabolite AC886 competitively bind to the adenosine triphosphate (ATP) binding pocket of FLT3 with high affinity. Quizartinib and AC886 inhibit FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and blocking FLT3-ITD-dependent cell proliferation.

Pharmacodynamic effects

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% confidence interval (CI): 26.6 ms] at the steady-state C_{max} of quizartinib (53 mg) during maintenance therapy.

Clinical efficacy and safety

The efficacy and safety of quizartinib vs. placebo was investigated in a randomised, double-blind, placebo-controlled, phase III study, QuANTUM-First. The study enrolled 539 adult patients between 18 and 75 years of age (25% were 65 years or older), who were newly diagnosed with FLT3-ITD positive AML, as determined prospectively by a clinical study assay. Patients were randomised (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 single-agent maintenance therapy 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 with either daunorubicin on days 1, 2 and 3 or idarubicin on days 1, 2 and 3 and cytarabine 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 on days 1, 3 and 5. Patients who proceeded to HSCT stopped receiving study treatment 7 days before the start of a conditioning regimen. Please refer to the Summary of Product Characteristics for daunorubicin, idarubicin and cytarabine dosing recommendations.

The two randomised treatment groups were well balanced with respect to baseline demographics, disease characteristics and stratification factors. Of the 539 patients, the median age was 56 years (range 20-75 years), 26.1% of patients in the quizartinib arm and 24% of patients in the placebo arm were 65 years or older; 54.5% were female and 45.5% were male; 59.7% were White, 29.3% were Asian, 1.3% were Black or African American, and 9.7% were other races. Eighty-four percent of patients had an Eastern Cooperative Oncology Group (ECOG) baseline performance status of 0 or 1. The majority of the patients (72.4%) had intermediate cytogenetics risk status at baseline. FLT3-ITD variant allele frequency (VAF) was 3-25% in 35.6% of patients, greater than 25-50% in 52.1% of patients and greater than 50% in 12.1% of patients.

The primary efficacy measure was overall survival (OS) defined as the time from randomisation until death from any cause.

The study demonstrated a statistically significant improvement in OS for the quizartinib arm (see Table 5 and Figure 1). The median follow-up time of the study was 39.2 months.

A difference was observed between the quizartinib arm vs. the placebo arm in the estimates of survival rates (95% CI) at the landmark timepoints of 12, 24, 36 and 48 months (see Table 5).

The complete remission (CR) rate [95% CI] for quizartinib was 54.9% (147/268) [48.7, 60.9] vs. 55.4% (150/271) [49.2, 61.4] for placebo.

Table 5: Efficacy results from QuANTUM-First (intent-to-treat population)

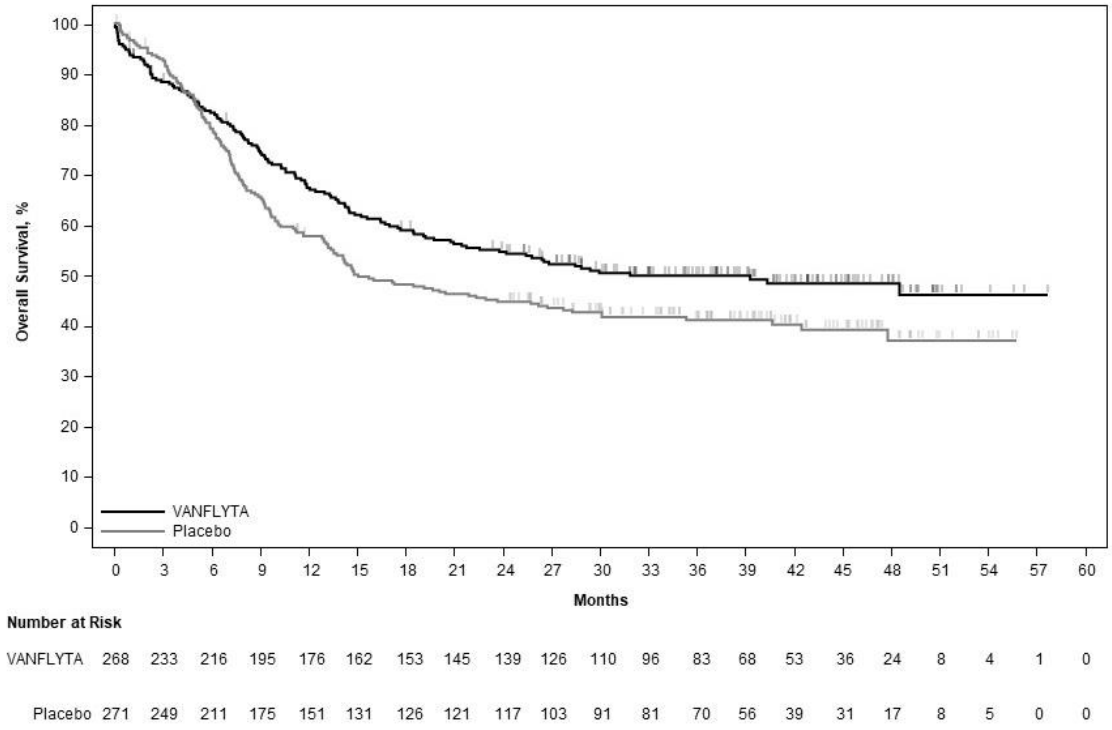
	Quizartinib N = 268	**Placebo N = 271**
OS (months)		
Median (95% CI)[a]	31.9 (21.0, NE)	15.1 (13.2, 26.2)
HR[b] relative to placebo (95% CI)	0.776 (0.615, 0.979)	
p-value (two-sided stratified log-rank test)	0.0324	
OS rate (%) (95% CI)[a]		
12 months	67.4 (61.3, 72.7)	57.7 (51.6, 63.4)
24 months	54.7 (48.4, 60.5)	44.7 (38.7, 50.6)
36 months	49.9 (43.7, 55.9)	41.1 (35.0, 47.0)
48 months	48.4 (41.9, 54.5)	37.0 (29.8, 44.2)

CI = confidence interval; NE = not estimable

[a] Kaplan-Meier estimate

[b] Hazard ratio (HR) was based on stratified Cox regression model.

Figure 1: Kaplan-Meier curves for overall survival in QuANTUM-First



Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with VANFLYTA in one or more subsets of the paediatric population in the treatment of acute myeloid leukaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

The absolute bioavailability of quizartinib from the tablet formulation was 71%. After oral administration under fasted conditions in healthy subjects, 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.

The administration of quizartinib with food, in healthy subjects, decreased quizartinib C_{max} by 1.09-fold, increased AUC_{inf} by 1.08-fold and t_{max} was delayed by two hours. These changes in exposure are not considered clinically relevant. VANFLYTA can be administered with or without food.

Based on population pharmacokinetic modelling in newly diagnosed AML patients, at 35.4 mg/day, steady state during induction therapy, the geometric mean (%CV) C_{max} of quizartinib and AC886 was estimated to be 140 ng/mL (71%) and 163 ng/mL (52%), respectively, and the geometric mean (%CV) AUC_{0-24h} was 2 680 ng•h/mL (85%) and 3 590 ng•h/mL (51%), respectively.

During consolidation therapy at 35.4 mg/day, steady state, the geometric mean (%CV) C_{max} of quizartinib and AC886 was estimated to be 204 ng/mL (64%) and 172 ng/mL (47%), respectively, and the geometric mean (%CV) AUC_{0-24h} was 3 930 ng•h/mL (78%) and 3 800 ng•h/mL (46%), respectively.

During maintenance therapy at 53 mg/day, steady state, the geometric mean (%CV) C_{max} of quizartinib and AC886 was estimated to be 529 ng/mL (60%) and 262 ng/mL (48%), respectively, and the geometric mean (%CV) AUC_{0-24h} was 10 200 ng•h/mL (75%) and 5 790 ng•h/mL (46%), respectively.

Distribution

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

The blood-to-plasma ratio of quizartinib and AC886 are concentration dependent, indicating saturation of the distribution to erythrocytes. At clinically relevant plasma concentrations, the blood-to-plasma ratio is approximately 1.3 for quizartinib and approximately 2.8 for AC886. Blood-to-plasma ratio of AC886 is also dependent on haematocrit, with a trend of increasing at higher haematocrit levels.

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

Biotransformation

Quizartinib is primarily metabolised by CYP3A4 and CYP3A5 *in vitro* via oxidative pathways which produces the active metabolite AC886, which is then further metabolised by CYP3A4 and CYP3A5. The steady-state AC886-to-quizartinib AUC_{0-24h} ratio during maintenance therapy was 0.57.

Elimination

The mean (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. The mean (SD) accumulation ratios (AUC_{0-24h}) for quizartinib and AC886 were 5.4 (4.4) and 8.7 (6.8), respectively.

Quizartinib and its metabolites are primarily eliminated by the hepatobiliary route with excretion mainly via faeces (76.3% of the orally administered radioactive dose). Unchanged quizartinib represented approximately 4% of the orally administered radioactive dose in faeces. Renal excretion is a minor route of elimination of the administered radioactive dose (< 2%).

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

Linearity/non-linearity

Quizartinib and AC886 showed linear kinetics 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.

Pharmacokinetic/pharmacodynamic relationships

Age (18 to 91 years), race, sex, body weight, or renal impairment (CLcr 30 to 89 mL/min, estimated by Cockcroft-Gault) did not have a clinically relevant effect on quizartinib and AC886 exposure based on a population pharmacokinetic analysis.

Interaction studies with other medicinal products

Transporters
In vitro studies showed that quizartinib is a substrate for P-gp but not for BCRP, OATP1B1, OATP1B3, OCT1, OAT2, MATE1 or MRP2. AC886 is a substrate for BCRP but not for OATP1B1, OATP1B3, MATE1 or MRP2. However, the single-dose administration of quizartinib with ketoconazole, a strong inhibitor for both CYP3A and P-gp, increased quizartinib C_{max} by approximately 1.17-fold, suggesting that the effect of P-gp is minimal. As dose adjustment is required for concomitant strong CYP3A inhibitors, many of which also inhibit P-gp, no specific dose adjustment is required for P-gp inhibitors.

Uridine diphosphate glucuronosyltransferases (UGT)1A1 substrates
Quizartinib inhibits UGT1A1 with an estimated *in vitro* Ki 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) by 1.03-fold which was not considered clinically relevant.

Special populations

Hepatic impairment
In a single-dose (26.5 mg) phase 1 study, 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) and compared to subjects with normal hepatic function. The exposure (C_{max} and AUC_{inf}) of quizartinib and AC886 were similar (≤ 30% difference) across all groups. Protein binding of quizartinib and AC886 is not affected by impaired hepatic function. Therefore, hepatic impairment did not have a clinically relevant 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) were not included in the clinical studies; therefore, VANFLYTA is not recommended for use in these patients.

Renal impairment
A population pharmacokinetic analysis in AML patients with mild to moderate renal impairment (CLcr 30 to 89 mL/min) showed that renal function did not affect quizartinib and AC886 clearance. Therefore, mild and moderate renal impairment did not have a clinically relevant 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 studies; therefore, VANFLYTA is not recommended for use in these patients.

5.3 Preclinical safety data

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 and did not induce polyploidy in a chromosome aberration assay and was not clastogenic or aneugenic in a single-dose rat bone marrow micronucleus assay. An *in vivo* bone marrow micronucleus assay in rats was equivocal after 28 days repeated dosing. After a single higher dose, the result was negative.

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 doses approximately 10 times the recommended human dose (RHD) based on AUC. Findings in female monkeys included atrophy of the uterus, ovary and vagina; observed at doses approximately 0.3 times the RHD based on AUC. The corresponding no observed adverse effect levels (NOAELs) for these changes were 1.5 times and 0.1 times the RHD, respectively, based on AUC. In male rats, testicular seminiferous tubular degeneration and failure of sperm release were observed at approximately 8 times the RHD based on AUC. Findings in male monkeys included germ cell depletion in the testes; observed at approximately 0.5 times the RHD based on AUC. The corresponding NOAELs for these changes were 1.4 times and 0.1 times the RHD, respectively, based on AUC. After a four-week recovery period, all these findings except the vaginal mucosal modifications in the female rats were reversible.

In embryo-foetal toxicity studies, embryo-foetal lethality and increased post-implantation loss were observed at maternally toxic doses. Foetotoxicity (lower foetal weights, effects on skeletal ossification) and teratogenicity (foetal abnormalities including oedema) were observed at doses approximately 3 times the RHD based on AUC. The NOAEL was 0.5 times the RHD based on AUC. Quizartinib is considered to be potentially teratogenic.

Animal toxicology studies

In repeat dose toxicity studies, haematopoietic and lymphoid organ toxicity were observed including decreased peripheral blood cells and bone marrow hypocellularity; liver toxicity including elevated aminotransferases, hepatocellular necrosis and birefringent crystal deposition (dogs); and kidney toxicity including tubular basophilia and birefringent crystal deposition (male rats). These changes were noted at approximately 0.4 times, 0.4 times and 9 times the RHD based on AUC, respectively. The corresponding NOAELs were approximately 0.1 times, 0.1 times and 1.5 times the RHD based on AUC, respectively.

In vitro and animal safety pharmacology studies

In cardiovascular safety pharmacology 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}. The NOAEL was approximately 0.4 times the RHD based on C_{max}. Quizartinib primarily inhibited I_{Ks} with a maximum inhibition of 67.5% at 2.9 μM. The maximum inhibition of I_{Ks} by AC886 was 26.9% at 2.9 μM. Quizartinib and AC886 at 3 μM statistically significantly inhibited hERG currents by 16.4% and 12.0%, respectively. Neither quizartinib nor AC886 inhibited I_{Na}, I_{Na-L} and I_{Ca-L} at any concentration tested.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

VANFLYTA 17.7 mg film-coated tablets

Tablet core
Hydroxypropylbetadex
Cellulose, microcrystalline (E460)
Magnesium stearate

Film-coating
Hypromellose (E464)
Talc (E553b)
Triacetin (E1518)
Titanium dioxide (E171)

VANFLYTA 26.5 mg film-coated tablets

Tablet core
Hydroxypropylbetadex
Cellulose, microcrystalline (E460)
Magnesium stearate

Film-coating
Hypromellose (E464)
Talc (E553b)
Triacetin (E1518)
Titanium dioxide (E171)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium perforated unit dose blisters.

VANFLYTA 17.7 mg film-coated tablets

Cartons containing 14 x 1 or 28 x 1 film-coated tablets.

VANFLYTA 26.5 mg film-coated tablets

Cartons containing 14 x 1, 28 x 1 or 56 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Daiichi Sankyo Europe GmbH
Zielstattstrasse 48
81379 Munich
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/23/1768/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1
85276 Pfaffenhofen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of VANFLYTA in each Member State, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at reinforcing the prescriber's and patient/caregiver's awareness about the risk of serious ADRs related to QTc interval prolongation, and the actions to be taken to minimise the occurrence of the risk in patients receiving VANFLYTA.

The MAH shall ensure that in each Member State where VANFLYTA is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe, dispense, and use VANFLYTA have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals will contain the following key elements:

- Description of serious ADRs related to QTc interval prolongation that have occurred with quizartinib
- Detailed description of the recommended VANFLYTA dosing regimen: starting dose and dose escalation criteria
- Detailed description of VANFLYTA dose interruption, dose reduction, and treatment discontinuation based on QTc interval duration
- VANFLYTA dose modification for concomitant strong CYP3A inhibitors use
- Management of other co-medications that are known to cause QT prolongation
- Frequency of ECG monitoring
- Serum electrolyte monitoring and management

The patient information pack:

- Package leaflet
- Patient card

The Patient card will contain the following key elements:

- A warning message for healthcare professionals that VANFLYTA treatment may increase the risk of serious ADRs related to QTc interval prolongation
- Important information for healthcare professionals not involved in the regular care of the patient about patient management related to QTc prolongation
- Important information for patients/caregivers about signs or symptoms of serious ADRs related to QTc interval prolongation and when to seek attention from a healthcare professional
- Contact details of the VANFLYTA prescriber

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 17.7 mg film-coated tablets
quizartinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 17.7 mg quizartinib (as dihydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 x 1 film-coated tablets
28 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Daiichi Sankyo Europe GmbH
81366 Munich, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1768/001 14 x 1 film-coated tablets
EU/1/23/1768/002 28 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vanflyta 17.7 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 17.7 mg tablets
quizartinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Daiichi-Sankyo (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 26.5 mg film-coated tablets
quizartinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 26.5 mg quizartinib (as dihydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 x 1 film-coated tablets
28 x 1 film-coated tablets
56 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Daiichi Sankyo Europe GmbH
81366 Munich, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1768/003 14 x 1 film-coated tablets
EU/1/23/1768/004 28 x 1 film-coated tablets
EU/1/23/1768/005 56 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vanflyta 26.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 26.5 mg tablets
quizartinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Daiichi-Sankyo (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PATIENT CARD

PATIENT CARD

VANFLYTA

quizartinib

- Please keep this card with you at all times.
- This card contains important safety information that you should know before you take VANFLYTA and during treatment with VANFLYTA.
- Show this card to any doctor, pharmacist or surgeon before any medical intervention or treatment.

Patient information

Patient name:
Date of birth:

In case of emergency, please contact:
Name:
Phone number:

Treatment information
(To be completed by physician or patient)

VANFLYTA has been prescribed at a once-daily dose of: mg
Started on: /(mm/yy)

Prescriber information
(To be completed by physician or patient)

For more information or in case of emergency, please contact:
Physician's name:
Phone number:

Important information for the patient

VANFLYTA can cause an abnormal electrical activity in your heart called 'prolonged QT interval' which may lead to a life-threatening disturbances of the heart rhythm. Therefore, a regular check of the electrical activity in your heart with an electrocardiogram (ECG) is very important.

Contact your doctor immediately if:

- You are feeling dizzy, lightheaded or faint.
- You sense a change in heart rhythm, e.g., palpitations or an abnormality of your pulse. You may feel your heart is beating too fast, but you may also sense a more nonspecific or vague change.
- You have fainted or have been unconscious, even if it was only for a very short period of time, e.g., seconds.
- You suffer from diarrhoea or vomiting, or are unable to eat or drink fluids in sufficient amounts.
- You feel any other sudden change in your well-being.
- Your medicines are changed by a physician other than the prescribing physician for VANFLYTA.

Consult your doctor first before taking VANFLYTA with any other medicines, including medicines obtained without a prescription or supplementary products as these may increase the risk of you developing QT interval prolongation.

For more information, please read the package leaflet.

Important information for healthcare professionals

VANFLYTA is associated with QT interval prolongation, which may increase the risk of ventricular arrhythmias or torsade de pointes.

- Interrupt VANFLYTA if QTcF is ≥501 ms and permanently discontinue if associated with torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of life-threatening arrhythmia. VANFLYTA is contraindicated in patients with congenital long QT syndrome.
- During VANFLYTA treatment, check serum electrolytes and correct any hypokalaemia and hypomagnesaemia as needed.
- Avoid non-essential medicines that prolong the QT interval. If unavoidable, monitor ECG frequently.
- The dose of VANFLYTA should be reduced when used concomitantly with strong CYP3A inhibitors.

For more information, please see the Summary of Product Characteristics (SmPC).

▼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. See the Patient Information Leaflet for how to report side effects.

Daiichi-Sankyo (logo)

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

VANFLYTA 17.7 mg film-coated tablets
VANFLYTA 26.5 mg film-coated tablets
quizartinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VANFLYTA is and what it is used for

What VANFLYTA is
VANFLYTA contains the active substance quizartinib. It is a type of cancer medicine called a 'protein kinase inhibitor'. The medicine is used along with chemotherapy to treat adults who have acute myeloid leukaemia (AML, a type of blood cancer), with a mutation (change) in the FLT3 gene called 'FLT3-ITD'. VANFLYTA treatment may be continued also after a bone marrow transplant when patients have sufficiently recovered.

Your doctor will test your cancer cells for changes in the FLT3 gene to look for FLT3-ITD mutations beforehand to make sure that VANFLYTA is right for you.

How VANFLYTA works
In AML, the body makes a large amount of abnormal white blood cells that do not mature to become healthy cells. VANFLYTA works by blocking the action of proteins called 'tyrosine kinases' in these abnormal cells. This slows down or stops the abnormal cells from dividing and growing uncontrollably, and helps immature cells grow into normal cells.

2. What you need to know before you take VANFLYTA

Do not take VANFLYTA
- if you are allergic to quizartinib or any of the other ingredients in this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you were born with a heart problem called 'long QT syndrome' (abnormal electrical activity of the heart that affects its rhythm).
- if you are breast-feeding (see 'Pregnancy, breast-feeding and fertility').

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking VANFLYTA:
- if you have or have had any heart problems including arrhythmia (abnormal heart rhythm), myocardial infarction (heart attack) within 6 months, congestive heart failure (heart isn't pumping hard enough), uncontrolled angina pectoris (chest pain) or uncontrolled hypertension (blood pressure that's too high).
- if you have been told you have low blood levels of potassium or magnesium.
- if you are taking medicines that can prolong the QT interval (irregular heart rhythm; see 'Other medicines and VANFLYTA').
- if you are taking strong CYP3A inhibitors (see 'Other medicines and VANFLYTA').
- if you have or have had fever, cough, chest pain, shortness of breath, tiredness or pain when urinating.

Monitoring during treatment with VANFLYTA
Blood tests
Your doctor will perform regular blood tests during treatment with VANFLYTA to check your blood cells (white blood cells, red blood cells, and platelets) and electrolytes (salts such as sodium, potassium, magnesium, calcium, chloride and bicarbonate in blood). Your doctor will check your electrolytes more often if you are experiencing diarrhoea or vomiting.

Electrocardiogram
Before and during your treatment, your doctor will check your heart with an electrocardiogram (ECG) to make sure your heart is beating normally. ECGs will be done weekly initially and less often thereafter as decided by your doctor. Your doctor will check your heart more often if you are taking other medicines that prolong the QT interval (see 'Other medicines and VANFLYTA').

Infections in patients older than 65 years
Elderly patients are at increased risk for very serious infections when compared to younger patients, especially in the early treatment period. If you are older than 65 years of age you will be closely monitored for the occurrence of severe infections during induction.

Children and adolescents
Do not give this medicine to children or adolescents below 18 years of age because there is not enough information about its use in this age group.

Other medicines and VANFLYTA
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, vitamins, antacids (medicines for heartburn and stomach acidity) and herbal supplements. This is because some medicines can affect how VANFLYTA works.

In particular, the following medicines may increase the risk of side effects with VANFLYTA by increasing the levels of this medicine in the blood:
- certain medicines used to treat fungal infections – such as itraconazole, posaconazole or voriconazole;
- certain antibiotics – such as clarithromycin or telithromycin;
- nefazodone, a medicine used to treat major depression.

The following medicines may reduce the effectiveness of VANFLYTA:
- certain medicines used to treat tuberculosis – such as rifampicin;
- certain medicines used to treat seizures or epilepsy – such as carbamazepine, primidone, phenobarbital or phenytoin;
- 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;

- 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.

Certain medicines use to treat HIV may either increase the risk of side effects (e.g., ritonavir) or reduce the effectiveness (e.g., efavirenz or etravirine) of VANFLYTA.

QT interval prolonging medicinal products
Co-administration of VANFLYTA with other medicinal products that prolong the QT interval may further increase the risk of QT prolongation. Examples of QT prolonging medicinal products include but are not limited to antifungal azoles, ondansetron, granisetron, azithromycin, pentamidine, doxycycline, moxifloxacin, atovaquone, prochlorperazine and tacrolimus.

Pregnancy, breast-feeding and fertility

Pregnancy

You should not take VANFLYTA during pregnancy. This is because it may harm your unborn baby. Women who are able to become pregnant should have a pregnancy test within 7 days before taking this medicine.

Women should use effective contraception during treatment with VANFLYTA and for at least 7 months after stopping treatment. Men should use effective contraception during treatment with VANFLYTA and for at least 4 months after stopping treatment.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

Breast-feeding

Do not breast-feed during treatment with VANFLYTA, and for at least 5 weeks after stopping treatment. This is because it is not known if VANFLYTA passes into your breast milk (see 'Do not take VANFLYTA'**)**.
If you are breast-feeding, ask your doctor, pharmacist or nurse for advice before taking this medicine.

Fertility

VANFLYTA may reduce fertility in women and men. You should discuss this with your doctor before starting treatment.

Driving and using machines
VANFLYTA is unlikely to affect your ability to drive or use machines.

3. How to take VANFLYTA

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much VANFLYTA to take
Your doctor or pharmacist will tell you exactly how much VANFLYTA to take. Do not change your dose or stop taking VANFLYTA without talking to your doctor first.

Usually you will start by taking 35.4 mg (two 17.7 mg tablets) once daily for 2 weeks during each cycle of chemotherapy. The maximum recommended dose is 53 mg once daily.

Your doctor may start you on a lower dose of one 17.7 mg tablet once daily if you are taking certain other medicines.

After your chemotherapy is completed your doctor may change your dose to one 26.5 mg tablet once daily for 2 weeks and then increase your dose to 53 mg (two 26.5 mg tablets) once daily going forward depending on how you respond to VANFLYTA.

Your doctor may temporarily interrupt treatment or change your dose based on blood tests, side effects or other medicines you may be taking.

Your doctor will discontinue your treatment if you are having a stem cell transplant. Your doctor will tell you when to stop taking your medicine and when to restart it.

Taking this medicine
- Take VANFLYTA by mouth - either with or without food.
- Take VANFLYTA at about the same time each day. This will help you remember to take your medicine.
- If you vomit after you take this medicine, do not take any more tablets until your next scheduled dose.

How long to take VANFLYTA
Continue taking VANFLYTA for as long as your doctor tells you. Your doctor will regularly monitor your condition to check that the treatment is continuing to work.

If you have any questions about how long to take VANFLYTA, talk to your doctor or pharmacist.

If you take more VANFLYTA than you should
If you accidentally take more tablets than you should, or if someone else accidentally takes your medicine, talk to a doctor straightaway or go to a hospital and take this package leaflet with you. Medical treatment may be necessary.

If you forget to take VANFLYTA
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.

Do not take an extra dose (two doses on the same day) to make up for a forgotten dose.

If you stop taking VANFLYTA
Stopping your treatment with VANFLYTA may cause your condition to become worse. Do not stop taking your medicine unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor, pharmacist or nurse immediately if you notice the following side effects:
- feeling dizzy, lightheaded or faint. These could be signs of a heart problem called ‘prolonged QT interval’ (abnormal electrical activity of the heart that affects its rhythm).
- fever, cough, chest pain, shortness of breath, tiredness or pain when urinating. These could be signs of an infection or febrile neutropenia (low white blood cell counts with fever).

Very common side effects
(may affect more than 1 in 10 people)
- Increase in alanine aminotransferase (abnormal liver enzyme results)
- Thrombocytopenia (low levels of blood platelets)
- Anaemia (low levels of red blood cells)
- Neutropenia (low levels of neutrophils, a type of white blood cell)
- Diarrhoea
- Nausea (feeling sick)
- Abdominal (stomach) pain
- Headache
- Vomiting
- Oedema (swelling of the face, arms and legs)
- Upper respiratory tract infections (nose and throat infections)
- Decreased appetite
- Epistaxis (severe nosebleeds)
- Fungal infections
- Herpes infections
- Dyspepsia (indigestion)
- Bacteraemia (bacteria in the blood)

Common side effects
(may affect up to 1 in 10 people)
- Pancytopenia (low levels in all types of blood cells)

Uncommon side effects
(may affect up to 1 in 100 people)
- Cardiac arrest (heart stops beating)
- Ventricular fibrillation (dangerous, irregular and uncoordinated contractions of the lower chambers of the heart)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VANFLYTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What VANFLYTA contains

- The active substance is quizartinib.
  VANFLYTA 17.7 mg: Each film-coated tablet contains 17.7 mg quizartinib (as dihydrochloride).
  VANFLYTA 26.5 mg: Each film-coated tablet contains 26.5 mg quizartinib (as dihydrochloride).
- The other ingredients are:
  VANFLYTA 17.7 mg:
  Tablet core: Hydroxypropylbetadex, microcrystalline cellulose, magnesium stearate
  Film-coating: Hypromellose, talc, triacetin, titanium dioxide
  VANFLYTA 26.5 mg:
  Tablet core: Hydroxypropylbetadex, microcrystalline cellulose, magnesium stearate
  Film-coating: Hypromellose, talc, triacetin, titanium dioxide, yellow iron oxide

What VANFLYTA looks like and contents of the pack

VANFLYTA 17.7 mg film-coated tablets (tablets) are white, round and with 'DSC 511' on one side, and available in cartons containing 14 x 1 or 28 x 1 film-coated tablets in aluminium/aluminium perforated unit dose blisters.

VANFLYTA 26.5 mg film-coated tablets (tablets) are yellow, round and with 'DSC 512' on one side, and available in cartons containing 14 x 1, 28 x 1 or 56 x 1 film-coated tablets in aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.