Summary of risk management plan for Vanflyta (quizartinib)

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of VANFLYTA is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of VANFLYTA in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Daiichi Sankyo (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of VANFLYTA.

Summary of risk management plan for VANFLYTA (quizartinib)

This is a summary of the risk management plan (RMP) for quizartinib. The RMP details important risks of quizartinib, how these risks can be minimised, and how more information will be obtained about quizartinib´s risks and uncertainties (missing information).

The SmPC and package leaflet for quizartinib give essential information to HCPs and patients on how quizartinib should be used.

Important new concerns or changes to the current ones will be included in updates of quizartinib's RMP.

I. The Medicine and What It Is Used For

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 ND AML that is FLT3-ITD positive (see SmPC Section Indications/Uses for the full indication). It contains quizartinib as the active substance, and it is given by oral administration.

Quizartinib is a potent oral second-generation Class III receptor tyrosine kinase inhibitor with potent activity against FLT3 both in vitro and in vivo. FLT3 is expressed in blood-forming precursor cells, and signalling through FLT3 promotes these cells' proliferation and differentiation. FLT3 is mutated in approximately 30% of subjects with AML; the mutations include ITD of the juxtamembrane domain of FLT3 and point mutations, usually in the kinase domain. Both types of mutations activate FLT3 and contribute to leukaemic transformation of blood-forming cells. Quizartinib selectively inhibits survival pathways that block cell death by inhibiting FLT3 receptor signalling. Quizartinib thus inhibits proliferation of FLT3-dependent cell lines.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of quizartinib, together with measures to minimise such risks and the proposed studies for learning more about quizartinib risks, are outlined below.

- Measures to minimise the risks identified for medicinal products can be the following:
  - Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs.
  - Important advice on the medicine's packaging.
  - The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
  - The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks. Together, these measures constitute routine risk minimisation measures. In the case of VANFLYTA, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below. In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of VANFLYTA is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of quizartinib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of quizartinib. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part VI Module II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Serious ADRs related to QTc interval prolongation Increased incidence of ADRs due to DDI with strong CYP3A inhibitors
Important potential risks	Embryo-foetal and reproductive toxicity
Missing information	Not applicable

ADR = adverse drug reaction; CYP = cytochrome P450; DDI = drug-drug interaction; QT = interval between the start of the Q wave and the end of the T wave; QTc = corrected QT interval

II.B Summary of Important Risks

Important identified risks include QTc interval prolongation/torsade de pointes, DDIs with strong CYP3A inhibitors. Important potential risks considered important for inclusion in the list of safety concerns include embryo-foetal and reproductive toxicity.

Important Identified Risk 1: Serious ADRs Related to QTc Interval Prolongation	
Evidence for linking the risk to the medicine	Dose dependent QTc prolongation was observed in the clinical development programme; QTcF prolongation was observed more frequently at quizartinib doses >60 mg. Approximately 28% of subjects had TEAEs of ECG QT prolonged; however, most of these cases were mild and were manageable with dose modification or electrolyte correction, and very few events were serious or led to study drug discontinuation. QTc interval prolongation is a risk factor for the development of severe or life-threatening cardiac arrhythmias, including torsade de pointes, which is associated with a significant risk of sudden cardiac death. Torsade de pointes or other ventricular arrhythmias have been infrequently reported in the quizartinib clinical development programme.
Risk factors and risk groups	Recognised risk factors for QTc prolongation include hypokalaemia, hypomagnesemia or hypocalcaemia, congenital long QT syndrome, concomitant use of antiarrhythmic medicinal products or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Other risk factors include baseline QT prolongation, subclinical long QT syndrome, cardiac history (eg, congestive heart failure, bradycardia, myocardial infarction), the elderly, and the female population. Individual patient risk factors

Important Identified Risk 1: Serious ADRs Related to QTc Interval Prolongation	
	for the development of torsade de pointes include congenital or acquired long QT syndrome, electrolyte abnormalities (hypokalaemia, hypomagnesemia, and hypocalcaemia), concomitant medications (eg, Class IA, Class IC, and Class III antiarrhythmic agents, phenothiazines, antiretroviral drugs, and tricyclic antidepressants), endocrine disorders, and cardiac disorders. Strong CYP3A inhibitors, such as azole antifungals, increase quizartinib plasma exposure. QTc interval prolongation has been shown to be dose and concentration dependent, and increased exposure to quizartinib can result in higher incidence of QTc interval prolongation.
Risk minimisation measures	Routine risk communication: None Routine risk minimisation measures: Contraindication section of the Product Information for subjects with congenital long QT syndrome. Inclusion in the list of ADRs in Undesirable effects section of Product information. Warnings and precautions section of Product information providing specific information on ECG monitoring, discontinuation, and/or reversibility. Dose adjustment guidelines in Dosage/Administration section of the Product information. Guidance on correction of electrolyte imbalance is described in section Warnings and precautions section of Product information. Additional risk minimisation measures: HCP Guide to reinforce prescriber's awareness about the risk of serious ADRs related to QTc interval prolongation and the risk minimisation measures. PC to ensure that special information regarding VANFLYTA and the risk of serious ADRs related to QTc interval prolongation is held by the patient at all times and reaches the relevant HCP as appropriate.
Additional pharmacovigilance activities	None

Important Identified Risk 2: Increased Incidence of ADRs due to DDI with Strong CYP3A Inhibitors	
Evidence for linking the risk to the medicine	Concomitant use of quizartinib with a strong CYP3A inhibitor increased the exposure of quizartinib and its active metabolite AC886 compared to the use of quizartinib alone in healthy volunteers. Coadministration of ketoconazole (200 mg twice daily for 28 days) with single-dose administration of quizartinib resulted in increased C_{max} by 17% and AUC_{inf} by 94%. At steady state, exposure (C_{max} and $AUC_{0\text{-}24h}$) was estimated to be increased by 86% and 96%, respectively. Increased quizartinib exposure may increase the risk of toxicity.
Risk factors and risk groups	No specific risk factors are identified.
Risk minimisation measures	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for quizartinib dose adjustment if concomitant use of strong CYP3A inhibitors is described in Dosage/Administration section of the Product information. Information on DDIs in Interaction section of the Product information. Additional risk minimisation measures: None

Important potential risks considered important for inclusion in the list of safety concerns include Embryo-Foetal and Reproductive Toxicity, as outlined below.

Important Potential Risk 1: Embryo-Foetal Reproductive Toxicity	
Evidence for linking the risk to the medicine	Based on findings in animals, quizartinib may cause embryo-foetal harm when administered to a pregnant woman. No cases of embryo-foetal toxicity were observed in the clinical development programme. Based on findings in animals, female and male fertility may be impaired with treatment with quizartinib.
Risk factors and risk groups	No specific risk factors have been identified.
Risk minimisation measures	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in Warnings and Precautions section of Product information on risk of embryo-foetal and reproductive toxicity in Pregnancy, Lactation section of Product information. Additional risk minimisation measures: None

II.C. Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

Not applicable.

II.C.2 Other Studies in Post-authorisation Development Plan

Not applicable.