CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216993Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216993
PDUFA Goal Date	July 24, 2023
Nexus TTT #	2022-1091, 2022-1093, 2022-1147
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP Wambui Kiruthi, Pharm.D., MPH, Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) Kate Oswell, M.A., Health Communication Analyst
Team Leader	Naomi Boston, Pharm.D. Barbara Bergquist, Pharm.D. (DMAMES)
Associate Director for REMS	Laura Zendel, Pharm.D., BCPS
Design and Evaluation	
Review Completion Date	July 12, 2023
Subject	Evaluation of Need for a REMS
Established Name	quizartinib
Trade Name	Vanflyta
Name of Applicant	Daiichi Sankyo, Inc.
Therapeutic Class	kinase inhibitor
Formulation(s)	17.7 mg and 26.5 mg tablets

Dosing Regimen:

VANFLYTA Initiation	Induction*	Consolidation†	Maintenance
	Starting on Day 8 **(for 7 + 3 regimen)‡**	**Starting on Day 6**	**Starting on Day 1**
Dose	35.4 mg orally once daily	35.4 mg orally once daily	• Administer 26.5 mg orally once daily Days 1 through 14 of the first cycle if QTcF is less than or equal to 450 ms. • Increase the dose to 53 mg once daily on Day 15 of the first cycle if QTcF is less than or equal to 450 ms. Maintain the 26.5 mg once daily dose if QTcF greater than 500 ms was observed during induction or consolidation.
Duration **(28-day cycles)**	Two weeks in each cycle (Days 8 to 21)‡	Two weeks in each cycle (Days 6 to 19)	• Once daily with no break between cycles for up to 36 cycles

*Patients can receive up to 2 cycles of induction.

† Patients can receive up to 4 cycles of consolidation.

‡ For 5 + 2 regimen as the second induction cycle, VANFLYTA will be given on Days 6 to 19.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Vanflyta (quizartinib) is necessary to ensure the benefits outweigh its risks. Daiichi Sankyo, Inc. submitted a New Drug Application (NDA) 216993 for quizartinib with the proposed indication in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, 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 as detected by an FDA-approved test. The FDA approved indication will be in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML that is FLT3 ITD-positive as detected by an FDA-approved test. The serious risks associated with quizartinib include QT prolongation, torsades de pointes, and cardiac arrest and embryo-fetal toxicity. The Applicant submitted a proposed communication plan (CP) REMS for this application. Based on feedback from the Agency, on April 17, 2023, the Applicant submitted a proposed REMS with elements to assure safe use (ETASU) for this application that consists of prescriber certification, pharmacy certification, an implementation system, and a timetable for submission of assessments of the REMS to ensure the benefits of quizartinib outweigh the risks of QT prolongation, torsades de pointes, and cardiac arrest.

The Division of Risk Management (DRM) and the Division of Hematologic Malignancies I (DHM1) agree that a REMS with ETASU is needed to ensure the benefits of quizartinib outweigh its risks**.** The risk of QT prolongation, torsades de pointes, and cardiac arrest associated with quizartinib are serious and severe. Two Special Government Employees independently concluded that the risk demonstrated in the trial and the unique mechanism of QT prolongation necessitated measures beyond labeling to effectively educate relevant healthcare providers that will prescribe quizartinib. It is necessary for prescribers to understand the unique mechanism of QT prolongation, risks of QT prolongation, torsades de pointes, and cardiac arrest, recommendations to mitigate these risks, and the need to counsel patients.

The goals of the VANFLYTA REMS are to mitigate the serious risks of QT prolongation, Torsades de Pointes, and cardiac arrest by ensuring that:

1. Prescribers are able to identify the unique QT prolonging mechanism of VANFLYTA.
2. Prescribers are able to identify the risk factors that are associated with Torsades de Pointes and cardiac arrest with VANFLYTA.
3. Prescribers are able to identify the importance of providing risk mitigation measures including QTc interval monitoring, electrolyte monitoring and repletion, avoidance of concomitant QTc prolonging medications, and dose modifications/dose interruptions when indicated

Prescribers must certify in the REMS by completing training and a knowledge assessment and attest to complying with the requirements of the REMS. Pharmacies must certify in the REMS and establish processes and procedures to verify the prescriber is certified prior to dispensing. In addition to the REMS, the Applicant will be required to conduct postmarketing studies to further evaluate the serious

risk of QTc prolongation with quizartinib. The risks of QT prolongation, Torsades de Pointes, and cardiac arrest will also be communicated in labeling using a boxed warning, warnings and precautions, and a medication guide. Dependent upon assessment findings, postmarketing requirement results, or data from other sources, FDA may modify the REMS or consider other regulatory actions.

1. Introduction

This review by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Vanflyta (quizartinib) is necessary to ensure the benefits outweigh its risks. Daiichi Sankyo, Inc. submitted a New Drug Application (NDA) 216993 for quizartinib with the proposed indication in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, 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 as detected by an FDA-approved test.[1] This application is under review in the Division of Hematologic Malignancies I (DHM1). The Applicant initially submitted a proposed communication plan (CP) REMS for this application. Based on the Agency's determination of the serious and severe risks of risks of QT prolongation, torsades de pointes, and cardiac arrest, and the unique mechanism of QT prolongation, the Applicant was informed that a communication plan REMS would not be sufficient to communicate these risks to relevant prescribers. On April 17, 2023, the Applicant submitted a proposed REMS with elements to assure safe use (ETASU) for this application that consists of prescriber certification and pharmacy (b) (4) certification, an implementation system, and a timetable for submission of assessments of the REMS to ensure the benefits of quizartinib outweigh the risks of QT prolongation, torsades de pointes, and cardiac arrest.

2. Background

2.1. Product Information

Vanflyta (quizartinib), a NME, is a kinase inhibitor. If approved, quizartinib will be indicated for use in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML that is FLT3 ITD-positive as detected by an FDA-approved test. Quizartinib is a small molecule inhibitor of the receptor tyrosine kinase FLT3. Quizartinib will not be indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); improvement in overall survival with quizartinib in this setting has not been demonstrated. Quizartinib and its major active metabolite AC886 bind to the adenosine triphosphate (ATP) binding domain of FLT3 with comparable affinity, and both had 10-fold lower affinity towards FLT3-ITD mutation compared to

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

FLT3 in a binding assay. Quizartinib and AC886 inhibited FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting downstream FLT3 receptor signaling and blocking FLT3-ITD-dependent cell proliferation. Quizartinib will be supplied as 17.7 mg and 26.5 mg tablets.

The proposed dosing of quizartinib is summarized below:[b]

VANFLYTA Initiation	Induction*	Consolidation†	Maintenance
	Starting on Day 8 (for 7 + 3 regimen)‡	**Starting on Day 6**	**Starting on Day 1**
Dose	35.4 mg orally once daily	35.4 mg orally once daily	• Administer 26.5 mg orally once daily Days 1 through 14 of the first cycle if QT interval corrected by Fridericia's formula (QTcF) is less than or equal to 450 ms. • Increase the dose to 53 mg once daily on Day 15 of the first cycle if QTcF is less than or equal to 450 ms. Maintain the 26.5 mg once daily dose if QTcF greater than 500 ms was observed during induction or consolidation.
Duration (28-day cycles)	Two weeks in each cycle (Days 8 to 21)‡	Two weeks in each cycle (Days 6 to 19)	• Once daily with no break between cycles for up to 36 cycles

*Patients can receive up to 2 cycles of induction.
† Patients can receive up to 4 cycles of consolidation.
‡ For 5 + 2 regimen as the second induction cycle, VANFLYTA will be given on Days 6 to 19.

Quizartinib was first approved outside of the United States in Japan in 2019. Quizartinib received fast track designation and was designated as an orphan product.

2.2. Regulatory History

The following is a summary of the regulatory history for quizartinib NDA 216993 relevant to this review:

- 03/18/2009: Orphan drug designation granted.
- 09/25/2018: NDA 212166 submission for the treatment of adults with relapsed or refractory AML which is FLT3 ITD-positive, as detected by an FDA approved test received.
- 05/14/2019: Oncologic Drugs Advisory Committee (ODAC) was convened to discuss whether the results of the OS analysis of Study AC220-007 are persuasive evidence of effectiveness of quizartinib. The AC voted 8 "no"/ 3 "yes" as answers to the voting question.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 06/14/2019: Complete Response (CR) letter sent to the Applicant due to Study AC220-007 not representing an adequate and well-controlled trial. In addition, the risks associated with quizartinib therapy from the clinical development program were not outweighed by the benefit of quizartinib therapy.
- 03/24/2022: Pre-NDA meeting with the Applicant where DHM1 agreed with Applicant to submit Communication Type REMS to facilitate review. The REMS should inform prescribers of cardiac toxicities of quizartinib including risks of concomitant use of drugs with QTc prolonging effect.
- 3/30/2022: Fast track designation granted.
- 08/24/2022: NDA 216993 submission on a new Phase 3 trial for treatment of adult patients with newly diagnosed AML that is FLT3 ITD-positive received. The Applicant submitted a communication plan REMS for quizartinib.
- 12/2/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the Agency is currently evaluating the proposed REMS regarding the cardiac toxicities of quizartinib.
- 02/27/2023, 03/06/2023: Meetings were held between the Agency and two separate Special Government Employees (SGEs) via teleconference to discuss the benefit-risk for the proposed indication, as well as the need for additional education and risk mitigation measures to prevent serious and potentially fatal arrhythmias.
- 03/27/2023: A meeting was held between the Agency and the Applicant via teleconference where the Agency informed the Applicant that a REMS with ETASU will be needed to ensure safe use of quizartinib.
- 04/17/2023: The Applicant submitted a REMS amendment that included an updated REMS document with ETASU, the REMS supporting document, and REMS materials.
- 04/19/2023: Major amendment letter sent to the applicant; PDUFA goal date extended by 3 months to July 24, 2023 due to the submission of a REMS with ETASU.
- 05/12/2023: The Agency sent an information request (IR) to the Applicant with general comments on the REMS website.
- 06/23/2023: The Agency sent an IR to the Applicant with comments on the REMS Document and REMS materials.
- 06/26/2023: The Applicant responded by email with clarifying questions regarding the IR. (b) (4) [redacted] and requested information on the submission of the final REMS in SPL format.
- 06/26/2023: The Agency responded via email regarding clarifying questions on the REMS resubmission, [redacted] (b) (4) and submission of the final REMS in SPL format within 14 days of approval is adequate.
- 06/27/2023: The Agency sent an IR to the Applicant with comments on the proposed Vanflyta REMS Assessment Plan.

- 06/29/2023: The Applicant submitted a REMS IR response including the REMS Document and REMS materials.
- 06/30/2023: The Applicant submitted a REMS IR response with the REMS Supporting Document and Vanflyta website post login screenshots.
- 07/06/2023: The Agency sent an IR to the Applicant with comments on the REMS Document and REMS materials**.**
- 07/06/2023: The Applicant responded by email with clarifying questions regarding the IR. The Applicant asked does the Agency not agree (b) (4) and is the proposed one-time REMS Authorization to Dispense (RDA) certification not acceptable?
- 07/06/2023: The Agency responded via email regarding clarifying questions on the REMS resubmission, that it does not agree (b) (4) but it does agree with the approach to use the same authorization code for each prescriber who has certified in the REMS program. Ensure that the RDA code is displayed on (b) (4) screens.
- 07/07/2023: The Agency sent an IR to the Applicant with comments on the REMS Supporting Document and the proposed Vanflyta REMS Assessment Plan**.**
- 07/10/2023: The Applicant submitted a REMS IR response including the REMS Document, REMS Supporting Document, and REMS materials.
- 07/11/2023: The Agency sent an IR to the Applicant with comments on the REMS Document and REMS materials**.**
- 07/11/2023: The Applicant submitted a REMS IR response including the REMS Document and REMS materials.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Acute myeloid leukemia is a hematologic malignancy characterized by uncontrolled proliferation of immature myeloid blood cells or blasts.[2,3,4] These malignant cells crowd the bone marrow leading to diminished hematopoiesis and peripheral cytopenias. In 2022, there were an estimated 20,050 new

cases and 11,540 deaths from AML in the U.S.[c] There is approximately 30.5% survival at 5 years.[d] *FLT3-ITD* activating mutation occurs in ~20-25% of adult patients with newly diagnosed AML. FLT3-IT positive AML is an aggressive form of AML associated with increased relapse rates and inferior survival.

3.2. Description of Current Treatment Options

Treatment of AML is initially approached with a question of ability to receive intensive therapy.[2,3,4] If a patient is deemed eligible, they are offered potentially curable therapy in the form of intensive chemotherapy. This has traditionally been termed "7+3" for the days of the regimen, where the 7 indicates the number of days of continuous cytarabine that is given and the 3 indicates the number of days that the patient is dosed with an anthracycline chemotherapeutic. This initial therapy given for 1-2 cycles is then followed by consolidation chemotherapy and/or allogenic HSCT. If patients are not able to receive intensive treatment due to advanced age or comorbidities, they can be offered several less intensive options that have shown clinical benefit in this setting but are not thought to induce long-term remissions (non-curative). Patients that are eligible and found to have an activating mutation in FLT3 are able to receive midostaurin in combination with their intensive chemotherapy regimen during the induction and consolidation phases. Rydapt (midostaurin), a kinase inhibitor, was approved by the FDA in 2017 for indications including treatment of adult patients with newly diagnosed AML that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.[5] The serious risks associated with midostaurin include embryo-fetal toxicity, pulmonary toxicity, and risk of prolonged severe neutropenia and thrombocytopenia in pediatric patients treated with combination chemotherapy. Midostaurin does not have a boxed warning in its label, and a REMS was not required for approval to ensure the benefits outweigh risks.

Despite availability of multiple therapies, AML is still a deadly disease. Only those patients that can tolerate intensive therapy have a chance for a cure while those that cannot tolerate such therapy will eventually succumb to the disease. Even with the approval of midostaurin for FLT3 mutant AML, only approximately 50% of patients have long term survival. There remains an unmet medical need in patients with newly-diagnosed FLT3-ITD mutated AML.

4. Benefit Assessment

The pivotal trial QuANTUM-First (NCT 02668653) supporting this application for efficacy and safety consisted of a Phase 3, randomized, double-blind, placebo-controlled study which evaluated quizartinib

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

vs placebo in patients with newly diagnosed FLT3-ITD positive AML.[1,4] Patients (N=539) were randomized to quizartinib (N=268) or placebo (n=271) in combination with induction and consolidation therapy and as maintenance monotherapy according to the initial assignment, as follows:

a) Induction: 35.4 mg orally once daily on Days 8-21 of 7 + 3 (cytarabine [100 or 200 mg/m^2/day] on Days 1 to 7 plus daunorubicin [60 mg/m^2/day] or idarubicin [12 mg/m^2/day] on Days 1 to 3) and on Days 8-21 or 6-19 of an optional second induction (7 + 3 or 5 + 2 [5 days cytarabine plus 2 days daunorubicin or idarubicin], respectively)
b) Consolidation: 35.4 mg orally once daily on Days 6-19 of high-dose cytarabine (1.5 to 3 g/m^2 every 12 hours on Days 1, 3 and 5) for up to 4 cycles
c) Maintenance: 26.5 mg orally once daily on Days 1 to 14 and 53 mg once daily thereafter for up to thirty-six 28-day cycles

The primary endpoint was overall survival (OS). Median OS was significantly longer for patients treated with quizartinib versus the placebo (hazard ratio [HR] 0.78; 95% confidence interval [CI] 0.62 to 0.98; p=0.0324). In an exploratory subgroup analysis of the 89/208 (43%) of patients who received maintenance therapy with quizartinib or placebo following consolidation chemotherapy, the OS HR was 0.40 (95% CI 0.19 to 0.84). Of 119/208 (57%) of patients who received maintenance therapy with quizartinib or placebo following HSCT, the OS HR was 1.62 (95% CI 0.62 to 4.22). The FDA clinical reviewer concluded that quizartinib was effective for the treatment of patients with newly-diagnosed FLT3-ITD positive AML when combined with induction and consolidation chemotherapy followed by maintenance therapy.[e] However, the efficacy of quizartinib maintenance post-HSCT was not established.

5. Risk Assessment & Safe-Use Conditions

The safety of quizartinib was evaluated in a Phase 3 clinical trial QuANTUM-First (NCT 02668653).[1,4,f] In the safety population, 265 patients received quizartinib and 268 patients received placebo with chemotherapy. Discontinuation due to a treatment emergent adverse event (TEAE) occurred in 20% in the quizartinib group and 9% in the placebo group. Common adverse reactions reported with quizartinib including laboratory abnormalities were lymphocytes decreased, potassium decreased, albumin decreased, phosphorus decreased, alkaline phosphatase increased, magnesium decreased, febrile neutropenia, diarrhea, mucositis, nausea, calcium decreased, abdominal pain, sepsis, neutropenia, headache, creatine phosphokinase increased, vomiting, and upper respiratory tract infection.

In study QuANTUM-First within 30 days of the last dose of study drug, 26 deaths were attributed to TEAE treatment related in the quizartinib group and 14 deaths were attributed to TEAE treatment

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

related in the placebo group.[4] There was one Grade 5 cardiac arrest on the quizartinib arm and there were no reported cases of cardiac arrest or Torsade de Pointes on the placebo arm. The Grade 5 event occurred in a 54 year old female patient who developed cardiac arrest on day 79 of treatment.

The serious risks[g] associated with quizartinib which include QT prolongation, torsades de pointes, and cardiac arrest and embryo-fetal toxicity are summarized in the sections below.

5.1. QT Prolongation, Torsades de Pointes, and Cardiac Arrest

Section 5 and a boxed warning in the draft labeling indicates that quizartinib prolongs the QT interval in a dose and concentration-dependent manner and torsades de pointes and cardiac arrest have occurred in patients treated with quizartinib. In the QuANTUM-First study, a QTcF greater than 500 ms occurred in 2.3% of patients receiving quizartinib, with a QTcF increase from baseline greater than 60 ms reported in 10% of patients. The mechanism of QTc interval prolongation with quizartinib is via inhibition of the slow delayed rectifier potassium current, I_{Ks}, as compared to all other medications that prolong the QTc interval, which is via the rapid delayed rectifier potassium current, I_{Kr}. The level of QTc prolongation with quizartinib that predicts the risk of cardiac arrhythmias is unclear. Inhibition of I_{Ks} and I_{Kr} which may occur if patients take quizartinib concomitantly with other QTc prolonging medications, may leave patients with limited reserve leading to a higher risk of QT prolongation and serious cardiac arrhythmias, including fatal outcomes. An Interdisciplinary Review Team for Cardiac Safety Studies consult indicated uncertainty whether the risk of fatal arrhythmias with quizartinib treatment can be managed through QTc interval monitoring alone.[6] In clinical trials with AML patients treated with quizartinib (N=1081), an adverse event of torsades de pointes occurred in approximately 0.2% of patients, cardiac arrest occurred in 0.6% including 0.4% with a fatal outcome, and ventricular fibrillation occurred in 0.1% of patients. These severe cardiac arrhythmias occurred predominantly during the induction phase of treatment.

The proposed label recommends:

- Avoid use in patients who are at significant risk of developing torsades de pointes, including uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, tachyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism.
- Do not initiate treatment with quizartinib if the QTcF interval is greater than 450 ms.

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- [redacted] (b) (4) in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome, or in patients with a history of ventricular arrhythmias or torsades de pointes.
- Perform an ECG and correct electrolyte abnormalities prior to initiation of treatment with quizartinib. During induction and consolidation, perform an ECG prior to initiation and then once weekly during quizartinib treatment or more frequently as clinically indicated. During maintenance, perform ECGs prior to initiation, once weekly for at least the first month following dose initiation and escalation, and as clinically indicated thereafter. Do not escalate the dose if QTcF is greater than 450 ms.
- Perform ECG monitoring of the QT interval more frequently in patients who are at significant risk of developing QT interval prolongation and torsades de pointes, or following dose escalation.
- Monitor and correct hypokalemia and hypomagnesemia prior to and during treatment with quizartinib, maintain electrolytes in the normal range, and monitor electrolytes and ECGs more frequently in patients who experience diarrhea or vomiting.
- Monitor patients more frequently with ECGs if coadministration of quizartinib with drugs known to prolong the QT interval is required.
- Reduce quizartinib if QTc increases to greater than 480 ms and less than 500 ms, interrupt and reduce quizartinib if QTc increases to greater than 500 ms, and permanently discontinue quizartinib in patients who develop recurrent QTc greater than 500 ms or QTc interval prolongation with signs or symptoms of life-threatening arrhythmia. [redacted] (b) (4)
- Reduce the quizartinib dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure.

To mitigate the serious risk of QT prolongation, torsades de pointes, and cardiac arrest, a REMS program that requires quizartinib only be available through this restricted program, and that prescribers and pharmacies must enroll in the program. In the REMS program, prescribers must counsel patients receiving quizartinib about the risk of QT prolongation, torsades de pointes, and cardiac arrest, and provide patients with a Patient Wallet Card.

5.2. Embryo-Fetal Toxicity

Quizartinib may cause fetal harm based on animal studies and the mechanism of action of the drug. Quizartinib has been reported to cause structural abnormalities and alterations to growth when administered to pregnant rats during organogenesis at exposures 3 times the maximum recommended human dose (MRHD) of 53 mg/day in animal reproduction studies. No clinical data is available with quizartinib in pregnancy in humans. The risk of embryo-fetal toxicity will be included in a Medication Guide and the warnings and precautions section of the label. The proposed label states to advise pregnant women of the potential risk to a fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status within seven days before starting quizartinib and that

effective contraception be used during treatment and for 7 months after the last dose. In addition, in males with female partners of reproductive potential, it is recommended that effective contraception be used during treatment and for 4 months after the last dose.

6. Expected Postmarket Use

Quizartinib will primarily be used in inpatient and outpatient settings. Quizartinib will be initiated after induction chemotherapy in inpatient settings, given after consolidation chemotherapy in outpatient settings, and maintenance given in outpatient settings.

The likely prescribers will be oncologists and hematologists with experience managing the serious adverse events reported with other therapies for hematologic malignancies which are associated with QTc prolongation approved without a REMS. However, two SGEs independently concluded that the risk demonstrated in the trial and the unique mechanism of QT prolongation necessitated measures beyond labeling to effectively educate the relevant healthcare providers that would be involved in prescribing quizartinib. Special Government Employee #1 noted that physicians would not appreciate the additional risk incurred by blockade of the slow potassium channel and SGE #2 noted that required education that clearly conveys the unique and serious risks of blockage of this alternative potassium channel would be critical to the safe use of quizartinib.

7. Risk Management Activities Proposed by the Applicant

To mitigate the risk of QT prolongation, torsades de pointes, and cardiac arrest, the Applicant submitted prescribing information that contained a boxed warning, a Medication Guide, and a Communication Plan (CP) REMS.

The Applicant submitted a CP REMS proposal on August 24, 2022 that included a REMS document, REMS materials and REMS Supporting Document. Based on communication the Applicant received from the Agency on March 27, 2023 that a REMS with ETASU A and B will be necessary to ensure safe use of quizartinib, the Applicant submitted a proposed REMS with ETASU on April 17, 2023. The Applicant's proposed REMS consists of ETASU including prescriber certification (A) and pharmacy (b) (4) certification (B), an implementation system, and a timetable for submission of assessments of the REMS to ensure the benefits of quizartinib outweigh the risks of QT prolongation, torsades de pointes, and cardiac arrest.

The sections below reflect the Applicant's initial proposed REMS submission on August 24, 2022 and on April 17, 2023. During the review of this application the Applicant has amended their proposal based on feedback from the review team. The REMS document in the appendix of this review reflects the final agreed upon REMS.

71 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRAD T MORIYAMA
07/13/2023 12:06:14 AM

BARBARA A BERGQUIST on behalf of WAMBUI G KIRUTHI
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07/13/2023 12:25:29 AM

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Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216993
Nexus ID Number	2023-4215
Submission Type/ Number	Original-1/36
Action Date	July 24, 2023
Reviewer Name(s)	Wambui Kiruthi, PharmD, MPH (DMAMES)
Team Leader	Barbara Bergquist, PharmD (DMAMES)
Review Completion Date	July 10, 2023
Subject	Memorandum Regarding the Proposed Vanflyta (quizartinib) Risk Evaluation and Mitigation Strategy (REMS) REMS Assessment Plan
Established Name	Vanflyta REMS
Name of Applicant	Daiichi Sankyo, Inc.
Therapeutic Class	Kinase Inhibitor
Formulation(s)	oral tablets
Submission Date	June 30, 2023

1. Introduction

This memorandum references our findings and recommendations for the proposed Vanflyta (quizartinib) Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan included in the REMS Supporting Document submitted April 17, 2023 and amended June 30, 2023. Specifically, the Applicant's response to our June 27, 2023 proposed REMS Assessment Plan revisions is the subject of this memorandum.

2. REMS Goal and Objectives

The proposed goals of the Vanflyta REMS are to mitigate the serious risks of QT prolongation, Torsades de Pointes, and cardiac arrest by ensuring that:

1. Prescribers are able to identify the unique QT prolonging mechanism of Vanflyta.
2. Prescribers are able to identify the risk factors that are associated with Torsades de Pointes and cardiac arrest with Vanflyta.
3. Prescribers are able to identify the importance of providing risk mitigation measures including QTc interval monitoring, electrolyte monitoring and repletion, avoidance of concomitant QTc prolonging medications, and dose modifications/dose interruptions when indicated.

3. ASSESSMENT PLAN

Revisions and editorial changes were needed to the Applicant's proposed Vanflyta REMS Assessment Plan included in their Supporting Document submitted on April 17, 2023[a] to capture additional data needed to inform whether the REMS is operating as intended and meeting its goal and objectives. The Applicant was provided feedback with suggested changes via an information request sent by DMAMES on June 27, 2023[b]. In response, the Applicant submitted an updated Assessment Plan in a June 30, 2023[c] submission.

Reviewer Comment: To note, the Applicant accepted most of the interim comments sent by Division of Mitigation Assessment and Medication Error Surveillance (DMAMES). The Applicant made additional proposed edits to the Assessment Plan. We do not object to the Applicants proposed additional changes to the Assessment Plan and rationales provided for revisions they did not accept; except for their revision (b) (4) *as noted below.*

[a] The REMS Supporting Document is located at:\\Cdsesub1\evsprod\NDA216993\0028\m1\us\116-risk-management-plan\rems-support-doc.docx.

[b] Kiruthi W, Bergquist B. Food and Drug Administration. Division of Mitigation Assessment and Medication Error Surveillance (DMAMES). Vanflyta (NDA 216993). Interim Comments for the Proposed Vanflyta (quizartinib) REMS on the REMS Assessment Plan, Audit Plan and Noncompliance Plan, Reference ID: 5198385. June 27, 2023. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806d97de

[c] The REMS Supporting Document is located at: \\CDSESUB1\EVSPROD\nda216993\0035\m1\us\116-risk-management-plan\rems-supporting-tracked-changes.docx \\CDSESUB1\EVSPROD\nda216993\0035\m1\us\116-risk-management-plan\rems-supporting-tracked-changes.docx

Of note, the Applicant did not agree with the Agency's recommendations (b) (4) *On July 6, 2023[d] the Applicant was notified that the Agency was not in agreement* (b) (4) *To align with the Agency's recommendation* (b) (4) *DMAMES communicated to the Applicant to re-submit an updated copy of the REMS Assessment Plan* (b) (4)*. The Applicant agreed and resubmitted these documents on July 7, 2023[f] via email. The resubmitted REMS Assessment Plan includes our recommended revisions and is acceptable. A copy of the Vanflyta REMS Assessment Plan submitted on July 7, 2023 via email is in Appendix A .*

Below summarizes the Applicant's actions in response to the Agency feedback that was provided on June 27, 2023 regarding the REMS Assessment Plan:

- *The Applicant agreed with our addition, "For each metric, the data will be provided for the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted" to the top of the assessment plan* (b) (4)
- *<u>Metric 1 Program Implementation</u>:*
  - *The Applicant revised* (b) (4) *to read "(provide data at the 1-year assessment only)".*
  - *The Applicant did not align metric 1d. to include only prescribers and pharmacies* (b) (4) *.*
  - *The Applicant did not align metric 1f. to include only pharmacies* (b) (4)
- *Metric 2 REMS Certification and Enrollment Statistics: The Applicant* (b) (4)

  Metric 2b was not updated to align with the REMS requirements of stakeholders (i.e. prescribers and pharmacies) that will be certified.
- *The Applicant added and proposed additional edits to the REMS Utilization Data metrics to the Vanflyta REMS to inform on the number of Vanflyta tablets sent, demographics of the healthcare providers who are prescribing, the types of pharmacies that are dispensing the product and the REMS Dispense Authorization (RDA) not issued. The new metric was numbered to be Metric 3. The new proposed metrics will capture:*
  - *"3. REMS Utilization Data*
    a. *Number of tablets sent to certified pharmacies, stratified by type of pharmacy*
    b. *Number and percentage of RDAs confirming initial healthcare provider certification generated by a certified pharmacy or healthcare setting stratified by medical specialty (e.g., oncology) and provider credentials (e.g., Doctor of Medicine)*
    c. *Number of dispense authorizations for initial healthcare provider certification confirmation stratified by pharmacy type*
    d. *Number of RDAs not issued due to the healthcare provider not certified.*
- *<u>Metric 3 REMS Compliance</u>:*
  - *Metric 3 was renumbered to be Metric 4.*

[d] Ryan, Sheila email communication to Gosberg, Andreas. July 6, 2023
[e] Ryan, Sheila email communication to Gosberg, Andreas. July 7, 2023
[f] Gosberg, Andreas email communication to Ryan, Sheila. July 7, 2023

- (b) (4) *Metric 3b was not updated to align with the REMS requirements of stakeholders (i.e. prescribers and pharmacies) that will be certified.*

- *Metric 4 REMS Coordinating Center Report:*
  - *Metric 4 was renumbered to be Metric 5.*
  - (b) (4) *Metric 4a was updated by the Applicant to read "Number of contacts by stakeholder type (certified Prescriber, certified Pharmacy or Healthcare Setting, Authorized Representative or staff, Wholesaler-Distributor)".*
- *Metric 5* (b) (4) *Metric 5 was renumbered to be Metric 6. The Applicant made additional edits to the Metric title. It was edited from* (b) (4) *to read "Knowledge Assessment". Editorial changes were made in the metric section where applicable.*
- *Metric 6 Knowledge, Attitude, and Behavior (KAB) Survey of Prescribers:*
  - *Metric 6 was renumbered to be Metric 7.*
  - *The Applicant accepted the recommendation to move the paragraphs that states "A KAB Survey will be conducted with random samples, if the population is large enough to randomize, of certified Prescribers who prescribe VANFLYTA. Note: If the REMS prescriber KAB survey sample size for Wave 1 is not achieved, the following measures will be taken to increase Prescribers response for future waves including personal telephone outreach to nonrespondents to encourage survey completion, increased survey field time, and/or increased honoraria, maintaining fair market value." to the REMS Supporting Document page 15 section titled "REMS Prescriber Knowledge, Attitude, and Behavior (KAB) Surveys". The Applicant also noted editorial changes were made where applicable to incorporate the updated title of* (b) (4) *to read "Knowledge Assessment".*
  - *The Applicant revised Metric 6a to align with the updated REMS objective from* (b) (4) *to "Evaluation of understanding of the risks and mitigation strategies of the VANFLYTA REMS as well as compliance with the mitigation strategies to include if prescribers are able to identify the unique QT prolonging mechanism of Vanflyta."*
  - *The Applicant revised Metric 6b to align with the updated REMS objective from* (b) (4) *to "Evaluation if prescribers are able to identify the risk factors that are associated with Torsades de Pointes and cardiac arrest with Vanflyta."*
  - *The Applicant revised Metric 6c to align with the updated REMS objective from* (b) (4) *to "Evaluation if prescribers are able to identify the importance of providing risk mitigation measures including QTc interval monitoring, electrolyte monitoring and repletion, avoidance of concomitant QTc prolonging medications, and dose modifications/dose interruptions when indicated."*

(b) (4)

- *Metric 8* (b) (4)
    - *The Applicant revised metric 8 to adequately capture the desired health outcomes. They proposed minor edits for the Metric* (b) (4) *to read "A summary analysis of all cases of severe and fatal QT prolongation, Torsades de Pointes, and cardiac arrest, stratified by source of report (e.g., spontaneous) reported in the United States to the Daiichi Sankyo global safety database."*
    - *The Applicant added metrics to also include the analysis if risk mitigation measures were taken. The applicant proposed the wording for the metric to read "The analysis will include an assessment whether the following risk mitigation measures were taken:*
        - *QTc interval monitoring*
        - *Electrolyte monitoring and repletion*
        - *Avoidance of concomitant QTc prolonging medications*
        - *Dose modification or interruptions when indicated"*
- *The Applicant added a metric titled Overall Assessment of REMS Effectiveness. The new metric was numbered Metric 9 and captured: "The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified."*
- *The Applicant updated Table 1. Vanflyta REMS Assessment Plan to align with the revisions.*
- *The Applicant is to submit their proposed prescriber Knowledge, Attitude, and Behavior (KAB) Surveys within 90-days post approval as a REMS Assessment Methodology for Agency Review.*

4. REMS SUPPORTING DOCUMENT

The Applicant revised the REMS Supporting Document to include revisions based on the June 27, 2023 Agency feedback and also proposed additional revisions. The Applicant included the following changes:

- The Applicant accepted Agency feedback (b) (4) The new section included updated KPIs, the KPI thresholds, along with the Applicant's supporting rationale, and plans to evaluate the REMS if the KPI is not met.
- For the REMS Operations KPI: (b) (4)
- For the REMS Evaluation of the Objective:
    - The Applicant accepted the recommended revisions to align the KPI with the updated goals to assess "knowledge of the importance of providing risk mitigation measures including QTc interval monitoring, electrolyte monitoring and repletion, avoidance of concomitant QTc prolonging medications, and dose modifications/dose interruptions when indicated".

- The Applicant also revised
  - the title of the KPI from (b) (4) to read "REMS Evaluation of the Primary Objective".
  - the threshold from (b) (4) to be "A threshold of ≥80% (average of all questions) is targeted for Prescriber KAB Survey respondents".

Reviewer Comment: The Applicant rejected the following suggested edits from the June 27, 2023 Agency feedback:

- (b) (4) *The Applicant provided their detailed rationale for the rejection to this edit* (b) (4)
- *Revision of the REMS Operation KPI from the recommended "99.9% of dispensed prescriptions were written by a certified Prescriber and dispensed by a certified Pharmacy" to align with the stakeholders that will be certified.* (b) (4) *The Applicant was asked to provide a rationale by July 10, 2023* (b) (4) *DMAMES will review their rationale when received. However, the Agency generally recommends a KPI threshold of no more than 99.9% to allow for human error in the dispensing process.*

We do not object to the Applicants proposed additional changes to the supporting document and rationales provided for revisions they did not accept with the exception of the KPI threshold as noted above. Of note, the amended REMS Supporting Document submitted via email on July 7, 2023 included the Agency's recommendation (b) (4) *. Additionally, the Agency defers comment on the Applicant's audit plan and non-compliance plan at this time as they were not reviewed as part of this submission. The Applicant is to submit their full audit plan and non-compliance plan within 60-days post-approval as a REMS Methodology for Agency review. The request for submission of these plans will also be included in the Approval Letter .*

5. Conclusion & Recommendations

The Vanflyta REMS Assessment Plan submitted by the Applicant on April 17, 2023 and amended on June 30, 2023 and July 7, 2023 (via email) is acceptable and no further revisions are needed at this time. The revised Vanflyta REMS Assessment Plan will be included in the Vanflyta Approval Letter (See Appendix A).

Evaluation of the REMS will include reporting on two key performance indicators; 1) a process indicator that will inform on whether the REMS is being implemented and operating as intended and 2) an outcome indicator that will evaluate the primary objective. Thresholds for the two KPIs have been set a priori and if met would indicate that the REMS is meeting its stated goal and objective.

The Vanflyta Approval Letter will instruct the Applicant to submit their full audit plan and non-compliance plan within 60-days post-approval as a REMS Assessment Methodology. The Applicant will also be asked to submit their proposed prescriber Knowledge, Attitude, and Behavior (KAB) Surveys within 90-days post approval as a REMS Assessment Methodology. DMAMES will conduct a review of these plans and KAB surveys at that time.

6. Comments to the Applicant

We have no comments for the Applicant at this time.

7. Appendix

Appendix A.

Vanflyta REMS Assessment Plan (*Extracted from July 7, 2023 REMS Supporting Document*)

The REMS Assessment Plan for VANFLYTA will include the data as summarized in Table 1. Data will be provided in a tabular format as appropriate.

For each metric, the data will be provided for the two previous, current, and cumulative reporting periods (where applicable), unless otherwise noted.

Program Implementation and Operations

1. Program Implementation (*provide data at the 1-year assessment only)
    a. *Date of first commercial availability of VANFLYTA
    b. Date the REMS Website went live
        i. Number of total visits and unique visits to the REMS Website
        ii. Number and type of VANFLYTA REMS materials downloaded or accessed
    c. *Date the REMS Coordinating Center was fully operational
    d. *Date Prescribers, and Pharmacies were able to complete the REMS certification process (online and by fax)
    e. *Date of the first Prescriber certification
    f. *Date of the first Pharmacy certification

2. REMS Certification and Enrollment Statistics
    a. Prescribers
        i. Number of newly certified Prescribers and number of active (i.e., who have prescribed VANFLYTA at least once during the reporting period) Prescribers stratified by:
            1. Credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician

Assistant, Other). If “other” accounts for > 10% of respondents for specialties, the most common specialties will be identified.
2. Specialty (e.g., Oncology, Hematology, Internal Medicine/Family Medicine, Other). If “other” accounts for > 10% of respondents for specialties, the most common specialties will be identified.
3. Geographic region as defined by the US Census
4. Method of enrollment (e.g., online, fax, e-mail) for newly certified Prescribers only

ii. Number of incomplete Prescriber enrollments, and summary of reported reason(s) for not completing

b. Pharmacies
   i. Number of newly certified Pharmacies and number of active (i.e., who have dispensed at least once during the reporting period) Pharmacies stratified by:
      1. Type of Pharmacy (i.e., Inpatient Hospital Pharmacy, Outpatient Hospital Pharmacy, Specialty Pharmacy, Other). If “other” accounts for > 10% of respondents for type, the most common type(s) will be identified.
      2. Geographic region as defined by the U.S. Census
      3. Method of enrollment (e.g., online, fax, e-mail) for newly certified Pharmacies only
   ii. Number of incomplete Pharmacy enrollments, and summary of reported reason(s) for not completing
c. Wholesalers-Distributors
   i. Number of Wholesalers-Distributors contracted to ship and number of active (i.e., have shipped) Wholesalers-Distributors

3. REMS Utilization Data
   a. Number of tablets sent to certified pharmacies, stratified by type of pharmacy
   b. Number and percentage of RDAs confirming initial healthcare provider certification generated by a certified pharmacy, stratified by medical specialty (e.g., oncology) and provider credentials (e.g., Doctor of Medicine)
   c. Number of dispense authorizations for initial healthcare provider certification confirmation stratified by pharmacy type
   ~~d.~~ Number of RDAs not issued due to the Healthcare provider not being certified.

4. REMS Compliance:
   a. Audits
      i. A copy of the Audit Plan
      ii. Report of audit findings for each stakeholder

iii. Number of audits expected, and the number of audits performed
iv. Documentation of completion of training for relevant staff at each audited stakeholder site
v. Documentation of processes and procedures for complying with the VANFLYTA REMS
vi. Verification for each audited stakeholder site that the designated Authorized Representative remains the same. If different, include the number of new Authorized Representatives
vii. Number and type of deficiencies noted for each group of audited stakeholders as a percentage of audited stakeholders
viii. Confirmation of documentation of completion of training for relevant staff after audit findings indicated training was necessary
ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

b. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder (Prescribers, Pharmacies and Wholesalers-Distributors), actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified from the REMS
    i. For those with deficiencies noted, report the number that successfully completed a Corrective and Preventive Actions (CAPA) plan within the timeframes specified in the Noncompliance Plan
    ii. For any that did not complete the CAPA within the timeframe specified in the Noncompliance Plan, describe actions taken
    iii. Number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
        1. Unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
        2. Source of the noncompliance data
        3. Results of root cause analysis
        4. Action(s) that were taken in response
    iv. Pharmacies
        1. Number of Pharmacies for which non-compliance with the VANFLYTA REMS is detected (numerator) divided by all Pharmacies dispensing VANFLYTA (denominator)
        2. Number and description of Pharmacies with no processes and procedures in place to verify Prescriber certification and any corrective and preventative actions taken to prevent future occurrences

3. Number of non-certified Pharmacies that dispensed VANFLYTA (numerator) divided by all Pharmacies that dispensed VANFLYTA
4. Number of prescriptions dispensed by non-certified Pharmacies (numerator) divided by all VANFLYTA prescriptions dispensed (denominator) and the actions taken to prevent future occurrences
5. Summary of audit findings and any action taken and outcome of actions to prevent future occurrences
6. Summary of findings for monitoring conducted during the reporting period, including any CAPA

v. Wholesalers-Distributors
1. Number and description of non-certified Pharmacies that were shipped VANFLYTA and the number of these that subsequently became certified
2. The number of contracted Wholesalers-Distributors for which non-compliance with the REMS was detected (numerator) divided by the number of contracted Wholesalers-Distributors (denominator)
3. The number of Wholesalers-Distributors not contracted with Daiichi Sankyo, Inc. that shipped VANFLYTA and the number of incidents for each
4. The number of contracted Wholesalers-Distributors suspended and/or unauthorized to distribute for non-compliance with REMS requirements and reasons for such actions

c. Any other VANFLYTA REMS noncompliance, source of report and resulting CAPA

5. REMS Coordinating Center Report
a. Number of contacts by stakeholder type (certified Prescriber, certified Pharmacy, Authorized Representative or staff, Wholesaler-Distributor)
b. Summary of the reasons for the call(s) by stakeholder type, limited to the top five reasons for calls by stakeholder group
c. Description of each call, including stakeholder credentials, which may indicate an issue with product access due to the REMS, REMS burden or adverse event
d. If the summary reason for the call(s) indicates an adverse event related to QT prolongation, Torsades de Pointes, or cardiac arrest, details and the outcome of the call(s)
e. An assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. The assessment will indicate whether the burden or access issue is attributable to the REMS, insurance, health care availability, or another reason

f. Summary of frequently asked questions (FAQ) by stakeholder credentials type, limited to the top five FAQs for calls by stakeholder group
g. Summary of any noncompliance that is identified through Coordinating Center contacts, source of report, and resulting CAPA
h. Summary of CAPAs resulting from issues identified
i. The shortest wait time for a call to be answered, the longest wait time for a call to be answered, and the median time for a call to be answered
j. Percentage of calls to the REMS Coordinating Center where the caller abandoned the call before the call was answered
k. The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned

Knowledge

6. Knowledge Assessment
    a. Number of completed Knowledge Assessments, including the method of completion
    b. Summary statistics, including mean number of attempts, scores, range of scores, and number of attempts to successfully complete the Knowledge Assessment
    c. Summary of most frequently missed questions on the Knowledge Assessment
    d. Summary of potential comprehension or perception issues identified with the Knowledge Assessment

7. Knowledge, Attitude, and Behavior (KAB) Survey of Prescribers

    a. Evaluation of understanding of the risks and mitigation strategies of the VANFLYTA REMS as well as compliance with the mitigation strategies to include if prescribers are able to identify the unique QT prolonging mechanism of Vanflyta.
    b. Evaluation if prescribers are able to identify the risk factors that are associated with Torsades de Pointes and cardiac arrest with Vanflyta.
    c. Evaluation if prescribers are able to identify the importance of providing risk mitigation measures including QTc interval monitoring, electrolyte monitoring and repletion, avoidance of concomitant QTc prolonging medications, and dose modifications/dose interruptions when indicated.

Health Outcomes and/or Surrogates of Health Outcomes (Safe Use Behaviors)

8. A summary analysis of all cases of severe and fatal QT prolongation, Torsades de Pointes, and cardiac arrest, stratified by source of report (e.g., spontaneous) reported in the United States to the Daiichi Sankyo global safety database. The analysis will include an assessment whether the following risk mitigation measures were taken:

    a. QTc interval monitoring
    b. Electrolyte monitoring and repletion
    c. Avoidance of concomitant QTc prolonging medications
    d. Dose modification or interruptions when indicated

Overall Assessment of REMS Effectiveness

9. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA A BERGQUIST on behalf of WAMBUI G KIRUTHI
07/10/2023 04:49:31 PM

BARBARA A BERGQUIST
07/10/2023 04:50:15 PM