

NDA 216993/S-003

SUPPLEMENT APPROVAL

Daiichi Sankyo, Inc.
Attention: Michael Sinks
Director, Regulatory Affairs
211 Mt. Airy Road
Basking Ridge, NJ 07920

Dear Michael Sinks:

Please refer to your supplemental new drug application (sNDA) dated October 31, 2025, received October 31, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vanflyta (quizartinib) tablets.

This Prior Approval sNDA provides for modifications to the approved Vanflyta risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Vanflyta (quizartinib) was originally approved on July 20, 2023. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of addition of a Pharmacy Guide, updates to the Pharmacy Enrollment form to identify additional pharmacy types, updates to the Prescriber Training Program to provide clarity for reporting responsibilities, and updates to the Prescriber Enrollment form to provide clarity for reporting responsibilities.

Your proposed modified REMS, submitted on October 31, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on July 20, 2023.

The revised REMS assessment plan must include, but is not limited to, the following:

For each metric, provide 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, Physician or Practice-owned Pharmacy (medical integrated dispensing practice), Other Entity that Dispenses and Distributes Vanflyta, 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
 - iii. The number of certified Pharmacies that both dispense to patients and distribute Vanflyta to other Pharmacies or entities within a health system, stratified by type of pharmacy
- c. Wholesalers-Distributors, and Other Entities
 - i. The total number of wholesalers, distributors, and other entities that distribute Vanflyta, stratified by other entities that distribute Vanflyta, wholesalers, distributors, other
 - ii. The total number of newly authorized wholesalers, distributors, and other entities that distribute Vanflyta, stratified by other entities that distribute Vanflyta, wholesalers, distributors, other
 - iii. The number of active (i.e., have shipped) wholesalers, distributors, and other entities that distribute Vanflyta, stratified by other entities that distribute Vanflyta, wholesalers, distributors, other

3. REMS Utilization Data

- a. Number of tablets sent to certified Pharmacies, stratified by type of pharmacy
- b. Number and percentage of REMS Dispense Authorizations (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 on 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 Compliance Plan which addresses the criteria for noncompliance for each stakeholder (Prescribers, Pharmacies, Wholesalers-Distributors, and Other Entities that distribute Vanflyta), 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 Compliance Plan
 - ii. For any that did not complete the CAPA within the timeframe specified in the Compliance 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 and Other Entities that distribute Vanflyta
 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 and other entities that distribute Vanflyta for which non-compliance with the REMS was detected (numerator) divided by the number of contracted Wholesalers-Distributors and other entities that distribute Vanflyta (denominator)
 3. The number of Wholesalers-Distributors and other entities that distribute Vanflyta not contracted with Daiichi Sankyo, Inc. that shipped Vanflyta and the number of incidents for each
 4. The number of contracted Wholesalers-Distributors and other entities that distribute Vanflyta suspended and/or unauthorized to distribute for non-compliance with REMS requirements and reasons for such actions
 - vi. Number of Patient Wallet Cards that were delivered by Daiichi Sankyo, Inc. field employees to healthcare providers
 - vii. Number of Patient Wallet Cards that were downloaded from the Vanflyta REMS Website
 - 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 and other entities that distribute Vanflyta)
 - 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. Prescriber Knowledge Survey

- 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 of 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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) If the new indication for use introduces unexpected risks: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

- e) If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use: Provision of as many of the currently listed assessment plan items as is feasible.
- f) If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.

Additionally, we recommend that you submit your proposed audit plan and noncompliance plan for FDA review within 60 days of this letter. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters, at the top of your cover letter and at the top of the first page of the main submission document: **“REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/ AUDIT AND NONCOMPLIANCE PLAN”**.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 216993 REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW
(insert concise description of content in bold capital letters, e.g.,
SURVEY METHODOLOGIES, AUDIT PLAN, NONCOMPLIANCE PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 216993 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR NDA 216993/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 216993/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 216993/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 216993/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 216993

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word and PDF format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format and PDF are preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

If you have any questions, contact Stacie Woods, Safety Regulatory Project Manager, at 301-796-4803 or stacie.woods@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Shan M. Pradhan, M.D.
Associate Director for Safety
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- REMS

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/

SHAN PRADHAN
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