NDA 216993

NDA APPROVAL

Daiichi Sankyo, Inc.
Attention: Andreas Gosberg, PhD
Director, Regulatory Affairs
211 Mount Airy Road
Basking Ridge, NJ 07920-2311

Dear Dr. Gosberg:

Please refer to your new drug application (NDA) dated August 24, 2022, received August 24, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VANFLYTA (quizartinib) tablets.

We acknowledge receipt of your major amendment dated April 17, 2023, which extended the goal date by three months.

This NDA provides for the use of VANFLTYA (quizartinib) 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 acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test.

Limitations of Use:

VANFLYTA is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); improvement in overall survival with VANFLYTA in this setting has not been demonstrated.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on May 1, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 216993**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for VANFLTYA (quizartinib) tablets shall be 60 months from the date of manufacture when stored at Controlled Room Temperature (20° - 25 °C).

ADVISORY COMMITTEE

Your application for VANFLYTA was not referred to an FDA advisory committee because the clinical trial design is acceptable.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are waiving the pediatric study requirement for ages birth to <1 month because necessary studies are impossible or highly impracticable. This is because in patients aged <1 month, AML with FLT3-ITD mutations is considered to occur too infrequently for a study to be feasible.

We are deferring submission of your pediatric study for ages ≥1 month to <18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. This required study is listed below.

4467-1 Conduct a clinical study to confirm the appropriate dose of quizartinib, and to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of quizartinib in combination with fludarabine and cytarabine, in pediatric patients ages ≥1 month to <18 years with relapsed/refractory FLT3-ITD positive AML. Patients should be followed for at least 12 months (52 weeks). Include at least 16 patients ≥1 month to <18 years old, including a minimum of 4 patients < 12 years old.

Interim Report Submission:	12/2025
Study Completion:	08/2030
Final Report Submission:	02/2031

Submit the protocol to your IND 074552, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of severe and fatal ventricular arrhythmia events in adult patients.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4467-2 Conduct an observational study using electronic health records (EHR) to further assess the risk of severe (Grades 3-4) and fatal ventricular arrhythmia events in adult patients treated with quizartinib for the indication of acute myeloid leukemia (AML) that is FLT3-ITD positive as detected by an FDA-approved test. The selected EHR data source should contain access to clinical data elements including ECG results, laboratory results, concomitant medications, and clinical data to allow for outcome validation (i.e., via chart review). Evaluate the incidence of severe and fatal arrhythmia events and collect detailed clinical features of the adverse reactions, to investigate associations and temporal relationships between the incidence and severity of arrhythmia events and other potential associated risk factors. Specify case definitions, measurement, validation methods, and procedures for all study outcomes.

The timetable you submitted on June 16, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2024
Final Protocol Submission:	11/2024
Interim Report Submission 1:	11/2025
Interim Report Submission 2:	11/2026
Interim Report Submission 3	11/2027
Interim Report Submission 4:	11/2028
Study Completion:	11/2029
Final Report Submission:	05/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess known serious risks of QTc prolongation and rates of Grade ≥3 adverse reactions including Grade ≥ 3 neutropenia, and to identify an unexpected serious risk of increased toxicity in patients with severe hepatic impairment.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4467-3 Conduct an exercise test study in healthy subjects to further evaluate the serious risk of QTc prolongation with quizartinib. Evaluate the impact of rapid acceleration in heart rate on the cardiac safety of quizartinib using a standardized test protocol such as Bruce protocol, modified Bruce protocol, or graded-intensity bicycle exercise test. Identify QT/QTc and RR intervals at rest, peak exercise, and recovery, and capture the incidence of arrhythmias and other adverse reactions.

The timetable you submitted on June 16, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2024
Final Protocol Submission:	09/2024
Study Completion:	10/2025
Final Report Submission:	04/2026

4467-4 Conduct a sub-maximal exercise test study in patients with AML to further evaluate the serious risk of QTc prolongation with quizartinib. Evaluate the impact of rapid acceleration in heart rate on the cardiac safety of quizartinib using a 24-Hour Holter study with sub-maximal exercise (e.g., postural provocation – i.e., supine to standing). Identify QT/QTc and RR intervals at rest and sub-maximal exercise and capture the incidence of arrhythmias and other adverse reactions. Include patients on beta-blockers in order to observe for mitigating effects on the incidence of quizartinib-related adverse reactions.

The timetable you submitted on June 16, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2024
Final Protocol Submission:	09/2024
Study Completion:	04/2027
Final Report Submission:	10/2027

4467-5 Conduct a randomized trial of quizartinib maintenance therapy that compares the recommended dosage of 53 mg daily to a lower dosage (e.g., 26.5 mg daily) to further characterize serious adverse reactions including but not limited to the rates of Grade ≥3 adverse reactions, Grade ≥ 3 neutropenia, QTc interval prolongation, and dose reductions, interruptions, and discontinuations due to adverse reactions and provide an analysis of dose- and exposure-response relationships for safety. Incorporate systematically assessed patient-reported outcome

assessments to further characterize safety and tolerability, including patient-reported symptoms, function, and overall side effect impact. Eligible patients will include newly diagnosed, FLT3-ITD positive AML patients in complete remission following consolidation and exclude patients who underwent allogeneic hematopoietic stem cell transplantation. The study should also provide an analysis of dose- and exposure-response relationships for efficacy, including overall survival and relapse-free survival.

The timetable you submitted on June 16, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2024
Final Protocol Submission:	09/2024
Interim Report Submission:	04/2029
Trial Completion:	09/2032
Final Report Submission:	03/2033

4467-6 Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of quizartinib and its metabolite AC886 and to determine appropriate dosing recommendations of quizartinib in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

The timetable you submitted on June 16, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2024
Final Protocol Submission:	09/2024
Trial Completion:	09/2025
Final Report Submission:	03/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 074552 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4467-7 Conduct exploratory analyses aimed at identifying potential mechanisms of primary and acquired resistance to quizartinib using longitudinal samples for cytogenetic and mutational analyses collected at baseline and at the end of treatment or time of relapse from patients treated with quizartinib in QuANTUM-First. Include a discussion of the results in the context of the available published literature.

The timetable you submitted on June 16, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	01/2024
Final Protocol Submission (Analysis Plan):	05/2024
Study Completion:	09/2024
Final Report Submission:	12/2024

4467-8 Conduct a clinical pharmacokinetic trial to assess the magnitude of decreased exposure of quizartinib and its metabolite AC886, and to determine appropriate dosing recommendations for quizartinib, with coadministration of a weak CYP3A inducer. Design and conduct the trial in accordance with the FDA Guidance for Industry: Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.

The timetable you submitted on June 16, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2024
Final Protocol Submission:	09/2024
Trial Completion:	01/2025
Final Report Submission:	07/2025

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 074552 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for VANFLTYA (quizartinib) to ensure the benefits of the drug outweigh the risks of QT prolongation, Torsades de Pointes, and cardiac arrest.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Vanflyta can be approved only if elements necessary to assure safe use are required as

part of the REMS to mitigate the risks of QT prolongation, Torsades de Pointes, and cardiac arrest listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies that dispense the drug are specially certified

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies that dispense the drug be specially certified.

Your proposed REMS, submitted on April 17, 2023, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce VANFLYTA into interstate commerce.

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

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.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed full audit plan and non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the prescriber knowledge survey for FDA review within 90 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 the first page of the submission:

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

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). 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, proposed 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 the 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 a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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.

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 REVISION 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 format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call contact, Sheila Ryan, PharmD, MPH, RAC, Senior Regulatory Health Project Manager, at (301) 796-2002 or sheila.ryan@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- 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/

MARC R THEORET
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