NDA 211810/S-6

SUPPLEMENT APPROVAL

Daiichi Sankyo, Inc.
Attention: Yoshiyuki Hattori, Ph.D.
Associate Director, Regulatory Affairs, Oncology
211 Mount Airy Road
Basking Ridge, NJ 07920

Dear Dr. Hattori:

Please refer to your supplemental new drug application (sNDA) dated and received October 22, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Turalio (pexidartinib) capsules.

This Changes Being Effected supplemental new drug application provides for proposed minor modifications to the approved Turalio (pexidartinib) 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 Turalio (pexidartinib) was originally approved August 2, 2019, and the most recent REMS modification was approved on August 4, 2020. The REMS consist of a communication plan, 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 changes to the Patient Status Form, Liver Adverse Event Reporting Form, Prescribing Training Slides, REMS Assessment Plan, and REMS website, to list gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) elevations and direct bilirubin (DBIL) elevations as a trigger for liver adverse event reporting suggestive of serious and potentially fatal liver injury, and to align these materials with the product label. REMS modifications were also made to the Patient Status Form and Liver Adverse Event Reporting Form to allow a more complete assessment of a patient's condition and treatment plan. The Patient Enrollment Form was also revised to provide more space for listing of a patient's medications.

Your proposed modified REMS, submitted on October 22, 2020, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on August 2, 2019.

The revised REMS Assessment Plan must include, but is not limited to, the following:

PROGRAM OUTREACH AND COMMUNICATION

1. Communication Plan (6-month, 1-year, and 2-year assessments only)
    a. Sources of the distribution lists for healthcare providers
    b. Number of healthcare providers targeted
    c. The date(s), number and medical specialty of healthcare providers who were sent the Letter for Healthcare Providers by the methods of distribution
    d. The date(s), number and names of Professional Societies that were sent the Letter for Professional Societies by the methods of distribution
    e. The number of mailings returned or undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients
    f. Professional meetings where TURALIO REMS materials were disseminated

PROGRAM IMPLEMENTATION AND OPERATIONS

2. REMS Program Implementation (6-month and 1-year assessments only)
    a. Date of first commercial distribution of TURALIO
    b. Date when the TURALIO REMS website became live and fully operational
    c. Date prescribers could become certified
    d. Date when pharmacies could become certified
    e. Date when patients could become enrolled
    f. Date when the REMS Call Center was established and fully operational

3. REMS Certification and Enrollment Statistics (provide previous, current, and cumulative reporting periods)
    a. Healthcare Providers
        i. Number of newly certified and active (i.e. who have prescribed at least once during the reporting period) healthcare providers stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), specialty (e.g., Oncology, Orthopedics, Other) and geographic region
        ii. Method of healthcare provider certification (online, fax or email)
    b. Pharmacies
        i. Number of newly certified and active (i.e. have received TURALIO) pharmacies stratified by geographic region

ii. Number of pharmacies that dispensed TURALIO stratified by geographic region
iii. Number of pharmacies that were unable to become certified and reason why

c. Patients
i. Number of newly enrolled patients stratified by age, gender, race, hepatic medical history, and geographic region
ii. Number of patients who have discontinued therapy and the reason for discontinuation

d. Wholesalers/Distributors
i. Number of newly enrolled and active (i.e., have shipped TURALIO) wholesalers/distributors

4. TURALIO Utilization Data (provide previous, current, and cumulative reporting periods)
a. Number of prescriptions (new and refills) dispensed stratified by:
i. Prescriber specialty, provider degree/credentials, geographic region
ii. Patient demographics (age, gender, race, and geographic region)
b. Number of unique patients receiving TURALIO, stratified by age, gender, race, and geographic region

5. REMS Infrastructure and Performance (provide previous, current, and cumulative reporting periods)
a. REMS Website
i. Number of visits and unique visits to the REMS website
ii. Number of REMS materials downloaded or printed for each material
b. Call Center Report
i. Number of contacts by stakeholder type (patient/caregiver, prescriber, pharmacy, wholesalers/distributors, other)
ii. Summary of reasons for calls (e.g., enrollment question) and by reporter (authorized representative, patient/caregiver, prescriber, other)
iii. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
iv. Summary of frequently asked questions (FAQ) by stakeholder type
v. A summary report of corrective actions resulting from issues identified
c. Report on ***Patient Status Forms***
i. Number of ***Patient Status Forms*** expected, received and outstanding as of the report cut-off date
ii. Number of first patient shipments sent prior to receipt of a ***Patient Enrollment Form***. Include outreach activities performed to collect the forms

iii. Number of ***Patient Status Forms*** not received within 20 calendar days of the date the last ***Patient Status Form*** was due. Include outreach activities performed to collect the forms
iv. Number of ***Patient Status Forms*** outstanding from previous reporting periods (if applicable)
v. Number of unique patients that experienced a treatment interruption, duration of the treatment interruption and reason for treatment interruption (e.g. liver toxicity, no status form received)
vi. Number of unique patients whose TURALIO was discontinued and the reason treatment was discontinued (e.g. liver toxicity, non-response to therapy, no status form received)

d. Report on ***Liver Adverse Event Reporting Form***
i. Number of ***Liver Adverse Event Reporting Forms*** expected due to a "yes" response on the ***Patient Status Form*** indicating that a form is required, received, and outstanding as of the report cut-off date
ii. Number of unique patients who had a ***Liver Adverse Event Reporting Form*** submitted

6. REMS Compliance (provide previous, current, and cumulative reporting periods)
a. Provide a summary of non-compliance identified, including but not limited to:
i. Provide a copy of the non-compliance plan, including the criteria for noncompliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS
ii. Provide a copy of the audit plan for each stakeholder
iii. Report of audit findings for each stakeholder (REMS Call Center, pharmacies and wholesalers/distributors)
1. The number of audits expected, and the number of audits performed
2. The number and types of deficiencies noted for each group of audited stakeholders
3. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit
4. For any that did not complete the CAPA within one month of the audit, describe actions taken
5. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time
6. Documentation of completion of training for relevant staff
7. The existence of documented processes and procedures for complying with the REMS
8. Verification that each audited stakeholder's site that the designated authorized representative remains the same. If

different, include the number of new authorized representatives and verification of the site's recertification

b. Prescribers (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
   i. The number of prescribers who were non-compliant with the TURALIO REMS program requirements
   ii. Number of prescribers that were de-certified and reasons for decertification. Include if any prescribers were re-certified

c. Patients
   i. Number of patients not enrolled in the REMS program or registry who were dispensed TURALIO

d. Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
   i. The number and type of pharmacy for which non-compliance with the REMS is detected
   ii. The number and type of non-certified pharmacies that dispensed TURALIO and the number of incidents for each
   iii. Number of TURALIO prescriptions dispensed that were written by noncertified prescribers and the actions taken to prevent future occurrences
   iv. Number of TURALIO prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences
   v. Number of TURALIO prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences
   vi. Number of times a TURALIO prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken
   vii. Number of TURALIO prescriptions dispensed for more than a 30 days' supply for each of the first three months of treatment
   viii. Number of pharmacies decertified, reasons for decertification, and actions to address non-compliance

e. Wholesalers/distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
   i. The number of authorized wholesalers/distributors for which noncompliance with the REMS is detected
   ii. Number of wholesalers de-enrolled, reasons for de-enrollment, and actions to address non-compliance
   ii. Number of times TURALIO was distributed to a non-certified pharmacy or directly to patients

HEALTH OUTCOMES AND/OR SURROGATES OF HEALTH OUTCOMES

7. Safety Surveillance (provide previous, current, and cumulative reporting periods)
   a. Known, or suspected adverse events related to serious and potentially fatal liver injury are to be reported regardless of outcome. Root cause analyses of whether periodic monitoring of liver function was followed per the ***Prescribing Information*** are to be included. Provide an overall analysis and discussion of all cases identified from all sources (i-vi) including but not limited to the following for each case: drug discontinued due to liver toxicity, drug withheld due to liver toxicity, pertinent clinical data (i.e. liver biochemical tests, liver biopsy, etc.), ALT or AST >3x ULN and TBIL >2x ULN, ALT or AST > 10x ULN with or without TBIL elevation, TBIL ≥2x ULN (or DBIL >1.5x ULN) without changes in ALT or AST, ALP >2x ULN with GGT >2x ULN, relevant comorbidities, prior and concomitant medications with hepatotoxic potential, treatment required, and clinical outcome. Sources of the reports are to include but not be limited to:
      i. Patient Status Form
         1. Number of cases of serious and potentially fatal liver injury adverse events reported on the ***Patient Status Form***, including a calculation of the event incidence.
         2. Number of patients who experienced more than one event.
         3. Trend analysis of whether adverse events decrease or increase over time.
      ii. Liver Adverse Event Form
      iii. Spontaneous adverse event reports
         1. Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest.
         2. Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report.
      iv. Literature searches
         1. Include the search strategy used to identify literature search cases.
         2. Include a line listing of all literature search cases that includes: reference, narrative, and assessment of causality.
      v. Social Media
   b. Include an overall analysis and discussion of information collected on the ***Patient Status Form*** and Adverse Event Liver Forms which further assesses the registry data with respect to the safe use and acute, chronic, and irreversible hepatotoxicity of TURALIO. Provide data in tabular format where applicable. Submit patient- level datasets with all variables collected and analytical programs compliant with current FDA standards, including appropriate define files and reviewer guides.

c. Include whether the data warrant further detailed assessment, labeling changes, and/or communication.

EVALUATION OF KNOWLEDGE

8. Post-Training Knowledge Assessments (provide previous, current, and cumulative reporting periods)
   a. Number of completed post-training Knowledge Assessments for prescribers including method of completion and number of attempts to complete
   b. Summary of the most frequently missed Knowledge Assessment questions
   c. A summary of potential comprehension or perception issues identified with the Knowledge Assessment

9. Stakeholder Surveys (beginning with the 1-year assessment report and annually thereafter with each assessment report)
   a. Prescriber surveys to assess if prescribers are educated on the following:
      i. the approved indication for TURALIO
      ii. the risk of serious and potentially fatal liver injury associated with the use of TURALIO
      iii. liver monitoring and dose modifications as described in the ***Prescribing Information***
      iv. the need to counsel patients about the risk of serious and potentially fatal liver injury, liver monitoring at baseline and periodically during treatment with TURALIO as described in the Patient Guide and to report signs and/or symptoms of liver injury to the physician during therapy

10. 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, 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 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 rational 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.

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 211810 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT 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.

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 211810 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 211810/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 211810/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 211810/ 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 211810/ 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 211810

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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

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

REPORTING REQUIREMENTS

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

If you have any questions, call Stacie Woods, Regulatory Health Project Manager, at 301-796-4803.

Sincerely,

{See appended electronic signature page}

Abhilasha Nair, M.D.
Associate Director for Safety (acting)
Office of Oncologic Diseases
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/

ABHILASHA NAIR
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