

NDA 211810

NDA APPROVAL

Daiichi Sankyo, Inc.
Attn: Sandra Hamelsky, Ph.D., M.P.H.
Director, Regulatory Affairs, Oncology
211 Mount Airy Road
Basking Ridge, NJ 07920-2311

Dear Dr. Hamelsky:

Please refer to your New Drug Application (NDA) dated November 30, 2018, received December 3, 2018, and to your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for TURALIO (pexidartinib), capsules, 200 mg.

This new drug application provides for the use of TURALIO (pexidartinib) capsules, 200 mg, for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

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](http://www.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.

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 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 April 12, 2019, 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 211810.**” Approval of this submission by FDA is not required before the labeling is used.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 hepatotoxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of hepatotoxicity. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

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- 3673 - 1 Conduct a long-term trial to further evaluate the risk of hepatotoxicity in adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery, who are receiving pexidartinib. The trial will include laboratory, imaging, and pathologic assessments of patients who experience liver toxicity due to exposure to pexidartinib. The trial should enroll patients with an AST or ALT > 3 x ULN with concomitant bilirubin >2 x ULN, an isolated bilirubin > 2 x ULN (excluding those with Gilbert's syndrome), or an isolated AST or ALT > 10 x ULN. The trial should evaluate the mechanism of action of liver injury based on liver biopsy information, including a detailed assessment of changes in resident macrophage phenotype, based on marker status, as well as detailed characterization of other immune cell infiltrates. Submit cumulative, integrated safety analyses after 5 and 10 years of follow-up from an adequate number of patients to characterize the long-term risk of hepatic failure with pexidartinib. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

The timetable you submitted on June 14, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/19
Final Protocol Submission: 06/20
Submission of 5-year Follow-up Analysis: 03/31
Submission of Final Study Report with 10-year Follow-up: 06/36

- 3673 - 2 Complete a pharmacokinetic trial to determine an appropriate dose of pexidartinib to minimize toxicity in patients with moderate hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf>

The timetable you submitted on June 14, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 10/19
Final Protocol Submission: 12/19
Trial Completion: 04/20
Final Report Submission: 09/20

- 3673 - 3 Complete a pharmacokinetic trial to determine the effect of a low-fat meal on the bioavailability of pexidartinib in accordance with the FDA Guidance

for Industry entitled "Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations" found at:
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM631941.pdf>

The timetable you submitted on June 14, 2019, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/19

3673 - 4 Complete a pharmacokinetic trial to determine the effect of a moderate CYP3A4 inhibitor on the exposure to pexidartinib in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies- Study Design, Data Analysis, and Clinical Implications" found at
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

The timetable you submitted on June 14, 2019, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/19

Submit clinical protocol(s) to your IND 117332 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:

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

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 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 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:

- 3673 - 5 Submit the final trial report and results from the ongoing DDI Study PL3397-AU126 evaluating the effect of pexidartinib on the exposure of midazolam (a CYP3A4 substrate) and tolbutamide (a CYP2C9 substrate).

The timetable you submitted on June 14, 2019, states that you will conduct this trial according to the following schedule:

Final Report Submission: 09/19

- 3673 - 6 Complete a pharmacokinetic trial or PBPK modeling to determine the effect of a moderate CYP3A4 inducer on the exposure to pexidartinib following single and multiple doses of pexidartinib in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies - Study design, Data Analysis, and Clinical Implications" found at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

The timetable you submitted on June 14, 2019, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/19

- 3673 - 7 Given the abundance of the ZAAD-1006a metabolite in human plasma following exposure to pexidartinib, assess the potential for off-target effects of ZAAD-1006a using in vitro screening assays (panels of kinases and receptors).

The timetable you submitted on June 19, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/19

Study Completion: 06/20

Final Report Submission: 09/20

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 117332 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 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 TURALIO to ensure the benefits of the drug outweigh the risks of serious and potentially fatal liver injury.

Your proposed REMS must also include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe TURALIO will support implementation of the elements of your REMS. The communication plan provides for the dissemination of information about the risk of serious and potentially fatal liver injury.

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that TURALIO can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious and potentially fatal liver injury listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- Each patient using TURALIO is subject to certain monitoring
- Each patient using the drug is enrolled in a registry

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 and practitioners that dispense the drug be specially certified.

Your proposed REMS, submitted on August 1, 2019, amended and appended to this letter, is approved.

The REMS consists of a communication plan, 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 TURALIO (pexidartinib) into interstate commerce.

The 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 websites
 - ii. Number of REMS materials downloaded or printed for each material

- b. Call Center Report
 - i. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesalers/distributors, other)
 - ii. Summary of reasons for calls (e.g., enrollment question) and by reporter (authorized representative, patient/caregiver, healthcare provider, 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 receipt of the last Patient Status Form for subsequent prescription refill shipments. 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 non-compliance 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 contact center, pharmacies and wholesalers/distributors).
 - The number of audits expected, and the number of audits performed
 - The number and types of deficiencies noted for each group of audited stakeholders
 - For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
 - For any that did not complete the CAPA within one month of the audit, describe actions taken.
 - Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
 - Documentation of completion of training for relevant staff
 - The existence of documented processes and procedures for complying with the REMS
 - 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. Healthcare Providers (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 healthcare providers who were non-compliant with the TURALIO REMS program requirements
 - ii. Number of prescriptions written by non-certified healthcare providers
 - iii. Number of healthcare providers that were de-certified and reasons for decertification. Include if any healthcare providers 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 non-certified 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 non-compliance with the REMS is detected
 - ii. Number of wholesalers de-enrolled, reasons for de-enrollment, and actions to address non-compliance
 - iii. 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 without changes in ALT or AST, 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
 - 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
 - Number of patients who experienced more than one event
 - Trend analysis of whether adverse events decrease or increase over time
 - ii. Liver Adverse Event Form
 - iii. Spontaneous adverse event reports
 - Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest
 - Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report
 - iv. Literature searches
 - Include the search strategy used to identify literature search cases
 - 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 healthcare providers 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. Healthcare Provider surveys to assess if healthcare providers 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). 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.*

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,

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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 CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

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

**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 000**

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, 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

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and*

*Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*³

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.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.⁷

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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, please contact the Regulatory Project Manager for this application within two weeks of receipt of this letter.

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

⁷ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

If you have any questions, call Nataliya Fesenko, Pharm.D., Regulatory Health Project Manager, at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

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ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
- Carton and Container Labeling
- REMS

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/s/

MARC R THEORET
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