NDA 022569/S-029

SUPPLEMENT APPROVAL

BTcP Pharma, LLC
c/o West Therapeutics Development, LLC
1033 Skokie Boulevard
Suite 620
Northbrook, IL 60062

Attention: Mahlaqa Patel
Vice President, Regulatory Affairs and Quality Assurance

Dear Ms. Patel:

Please refer to your supplemental new drug application (sNDA) dated and received July 25, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lazanda (fentanyl) Nasal Spray.

We also refer to our REMS MODIFICATION NOTIFICATION letter, dated March 27, 2019, informing you that the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) must be modified to ensure that the benefits of the drug outweigh its risks. This determination was based on information contained in the REMS assessment reports suggesting many patients prescribed a TIRF medicine may not have been opioid-tolerant when they received a new prescription for a TIRF medicine, as well as recommendations from the August 3, 2018, joint meeting of the Drug Safety and Risk Management, and the Anesthetic and Analgesic Drug Products advisory committees.

This supplemental new drug application proposes REMS modifications required under section 505-1 of the FDCA, consistent with those outlined in the March 27, 2019, letter.

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for TIRF products, of which Lazanda is a member, was originally approved on December 28, 2011, and the most recent REMS modification was approved on September 7, 2017. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Lazanda outweigh its risks, we determined that you were required to make the REMS modifications outlined in our REMS Modification letter dated March 27, 2019.

Your proposed modified REMS, submitted to Drug Master File (DMF) (b) (4) on December 7, 2020, and appended to this letter, is approved.

The modifications to the approved REMS must be fully implemented within 120 calendar days of the date of this letter.

The REMS uses a shared system for the elements to assure safe use, an implementation system, and a timeable for assessments of the REMS. This shared system, known as the TIRF REMS program, currently includes products listed on the FDA REMS, website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to 12 months from the date of the approval of this REMS modification (December 23, 2020) and annually thereafter.

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

Program Outreach and Communication

1. **Communication (1-year assessment post-modification approval only)**
    a. Sources of the distribution list(s) for the Dear Healthcare Provider Letter to healthcare providers likely to prescribe TIRF medicines
    b. Number of targeted healthcare providers who can prescribe
    c. The number of Dear Healthcare Provider letters sent by date(s), medical specialty, and method of distribution.
        i. The number and percentage of emailed letters successfully delivered, opened, and unopened.
        ii. The number and percentage of mailed letters successfully delivered or returned as undeliverable.
        iii. The number and percentage of faxed letters successfully delivered or returned as undeliverable.
    d. The number of professional societies sent the Dear Healthcare Provider Letter by date(s) and method of distribution. In addition, include which

professional societies distributed the Dear Healthcare Provider Letter or the content of the letter to their respective members.

e. Sources of the distribution list(s) for the Dear Pharmacy Letter to inpatient and outpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines

f. The number of pharmacies sent the Dear Pharmacy Letter date(s), type of pharmacy, and by method of distribution

   i. The number and percentage of emailed letters successfully delivered, opened, and unopened.

   ii. The number and percentage of mailed letters successfully delivered or returned as undeliverable.

   iii. The number and percentage of faxed letters successfully delivered or returned as undeliverable.

g. The number of professional societies sent the Dear Pharmacy by dates(s) and by method of distribution. In addition, include which professional societies distributed the Dear Pharmacy Letter or the content of the letter to their respective members.

h. Date(s) and name(s) of Professional meetings where TIRF REMS materials were disseminated or displayed.

Program Implementation and Operations

2. REMS Program Implementation (1-year assessment post-modification approval only)

a. Date when the modified TIRF REMS website went live and was fully operational

b. Date when healthcare providers who can prescribe could become certified in the modified REMS

c. Date when pharmacies could become certified in the modified REMS

d. Date when patients could be enrolled in the modified REMS

e. Date when distributors/wholesalers could be registered in the modified REMS

f. Date when the REMS Call Center for the modified TIRF REMS program went live and was fully operational

3. REMS Certification and Enrollment Statistics (provide previous, current, and cumulative reporting periods)

a. Patients (number and percent)

   i. For the one-year assessment report only:

1) Patients previously enrolled in the TIRF REMS Access program (i.e. enrolled prior to implementation of the modified REMS)

2) Patients re-enrolled (i.e., previously enrolled in the TIRF REMS Access program and transitioned to new program)

ii. Newly enrolled into the new program

iii. Active patients (i.e., received at least one dispensation of a TIRF product during the reporting period)

iv. For metrics 3.a.i. through iii, stratify by demographics (age, gender, ethnicity, race, and geographic region [as defined by US Census]), around-the-clock opioid(s) (moiety, daily dose, and duration of greater than seven days), medical reasons related to pain (cancer or non-cancer pain), TIRF medicine use in the prior six months, and concomitant benzodiazepines and other central nervous system (CNS) depressants

v. A summary of the methods of patient enrollment (e.g., online, fax)

vi. Number of patients who were unable to become enrolled, accompanied by a summary of the reasons they were unable to be enrolled

b. Healthcare Providers who can Prescribe (number and percent)

i. For the one-year assessment report only:

1) Healthcare providers who can prescribe who previously certified in the TIRF REMS Access program (i.e. enrolled prior to implementation of the modified REMS)

2) Healthcare providers who can prescribe who re-certified (i.e., previously certified in the TIRF REMS Access program and transitioned to new program)

ii. Healthcare providers who can prescribe who are newly certified

iii. Active prescribers (i.e. who have prescribed a TIRF at least once during the reporting period)

iv. For metrics 3.a.i. through iii, stratify by credentials, (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), medical specialty (e.g., Pain Medicine, Oncology, Internal Medicine, Other, etc.) and geographic region [as defined by US Census])

v. A summary of the methods of healthcare provider certification (e.g., online, fax)

vi. Number of healthcare providers who can prescribe who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

vii. For the 2-year assessment report, conduct an outreach to healthcare providers that did not re-certify in the REMS to ascertain the reasons why they did not re-certify. Submit the methodology protocol 120 days prior to initiating the outreach.

c. Pharmacies (number and percent)

i. For the one-year assessment report only:

1) Pharmacies previously certified in the TIRF REMS Access program (i.e. enrolled prior to implementation of the modified REMS)

2) Pharmacies re-certified (i.e., previously certified in the TIRF REMS Access program and transitioned to new program)

ii. Pharmacies newly certified into the new program

iii. Active pharmacies (i.e., have dispensed a TIRF at least once during the reporting period)

iv. For metrics 3.a.i. through iii, stratify by pharmacy type (inpatient, chain, independent [retail, mail, institutional], or closed system [provide identity of closed system entities]) and by geographic region [as defined by US Census])

v. A summary of the methods of pharmacy certification (e.g., online, fax)

vi. Number of pharmacies that were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

vii. For the 2-year REMS assessment report, conduct an outreach to pharmacies that did not re-certify in the REMS to ascertain the reasons why they did not re-certify. Submit the methodology protocol 120 days prior to initiating the outreach.

d. Wholesalers-Distributors (number)

i. Previously enrolled (i.e. enrolled prior to implementation of the modified REMS)

ii. Re-enrolled (i.e., enrolled prior to implementation of the modified REMS and transitioned to new program)

iii. Newly enrolled into the new program

iv. Active (i.e., distributed a TIRF product during the reporting period)

4. **TIRF Utilization Data (provide previous, current, and cumulative reporting periods)**
    a. Number of prescriptions/transactions authorized for dispensing and those dispensed stratified by:
        i. Prescriber specialty, degree/credentials, and geographic region.
        ii. Pharmacy type (specialty, central fill, inpatient, chain, independent [retail, mail, institutional], or closed system [provide identity of closed system entities])
        iii. Patient demographics (age, gender, ethnicity, race, and geographic region [as defined by US Census])
        iv. Identify the source of this information
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. REMS program Call Center Report
        i. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesalers/distributors, other)
        ii. A table summarizing the most frequently asked questions (e.g., enrollment question) and by stakeholder type (e.g., patient/caregiver, healthcare provider, pharmacy, wholesalers/ distributors, etc.).
        iii. Summary of reasons for calls (e.g., enrollment question) and by reporter (authorized representative, patient/caregiver, healthcare provider, other)
        iv. 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
        v. Summary of frequently asked questions (FAQ) by stakeholder type
        vi. A summary report of corrective actions resulting from issues identified
    c. Infrastructure Performance
        i. Number of times a backup system was used with reason(s) for each instance (for example, pharmacy level problem, or REMS

database problem) clearly defined and described with description of corrective actions taken

ii. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions

6. REMS Compliance (current reporting period)

a. Audits of pharmacies, wholesalers/distributors, and the REMS program Call Center) will be conducted to ensure that all REMS processes and procedures are in place, functioning, and support the REMS program, and will be submitted with each assessment report. The audit reports are to include:

i. A copy of the audit plan used for the reporting period

ii. A detailed description of audit findings including the number with no findings, minor, moderate, or serious findings; include information about the root cause of the noncompliance

iii. Number of audited sites in each stakeholder category listed directly above.

iv. Number of audits expected, and the number of audits performed

v. Number and types of deficiencies noted for each group of audited stakeholders

vi. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.

vii. Documentation of completion of training for relevant staff

viii. The existence of documented processes and procedures for complying with the REMS

ix. Verification that at each audited stakeholder's site, the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification.

x. For inpatient hospital pharmacies, also report:

1) The number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12-month period

2) Verification that processes such as order sets/protocols are in place to assure compliance with the REMS

xi. For closed systems, also report:

1) Numbers of prescription authorizations per closed system;

2) Numbers of prescriptions dispensed that did not receive REMS authorization

xii. Describe any corrective actions taken for any non-compliance as identified above during the audits as well as preventative measures that were developed because of uncovering these non-compliance events

1) For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of the audit.

2) For any that did not complete the CAPA within one month of the audit, describe additional actions taken.

b. Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as the Non-Compliance Working Group

c. For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, if any patient harm resulted, and any corrective actions taken. Also provide a summary of non-compliance identified by stakeholder, including but not limited to:

i. For Prescribers, provide:

1) Number of prescribing healthcare providers who were non-compliant with TIRF REMS requirements

2) Number of prescriptions written by non-certified healthcare providers

3) Number of healthcare providers that were suspended or de-certified and reasons for decertification. Include if any healthcare providers were re-certified.

ii. For Pharmacies provide:

1) Number and types of pharmacies for which non-compliance with the REMS is detected

2) Number and type of non-certified pharmacies that dispensed TIRFs and the number of incidents for each

3) Number of TIRF prescriptions dispensed that were written by non-certified prescribers and include steps taken to prevent future occurrences

4) Number of prescriptions dispensed by non-certified pharmacies and include steps taken to prevent future occurrences

5) Number of times certified pharmacies dispensed TIRFs to unenrolled patients

6) Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events occurred and were identified

7) Number of TIRF prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences

8) Number of pharmacies suspended or decertified by pharmacy type, the reasons for such actions, and actions to address non-compliance

iii. For Wholesalers/distributors provide:

1) The number of enrolled wholesalers/distributors for which non-compliance with the REMS is detected

2) Number of times TIRF products were distributed to a non-certified pharmacy or directly to patients, and actions taken to recover the TIRF product

3) Number of wholesalers suspended or de-enrolled, reasons for such action, and actions to address non-compliance

iv. For patients provide:

1) Number of patients unenrolled, and reasons for such

2) Number of patients not enrolled in the REMS who were dispensed TIRFs

d. For each non-patient stakeholder referred to in section 6.c. above:

i. Describe any moderate or serious non-compliance with the REMS that occurred during the first year of transitioning to the modified REMS

ii. Provide an assessment of stakeholder compliance in following the proposed transition plan in transitioning to the modified REMS

e. For each reporting period, include a copy of the non-compliance plan used during that reporting period

f. Number of times a TIRF was prescribed to an opioid non-tolerant individual by falsifying information. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified

Safe Use Behaviors

7. Patient Enrollment and Patient Status and Opioid Tolerance Forms

a. Report on the Patient Enrollment Form and Patient Status and Opioid Tolerance Form (the "Forms") (data presented for each individual form as well as combined):

i. (For the 1-, 2-, and 3-year assessment reports only) The most common modes of submission of Forms to the REMS (e.g., Fax, online)

ii. Number of Forms received compared to the number of TIRF prescriptions authorized for dispensing

1) Explain any discrepancies between these two metrics

2) Provide a description of the outcome/resolution of such event

iii. Provide an analysis of cases where multiple submissions of a Form for the same patient were required prior to the pharmacy dispensing a prescription:

1) Provide the mean, median, and range of the number of re-submissions

2) Provide the reason(s) for the re-submissions grouped by commonly encountered situations

3) Include an analysis of the number of Forms that were submitted that indicated that the patient was not opioid tolerant

iv. Number of Forms submitted to the REMS with incomplete, erroneous, or altered fields; provide:

1) An accounting of the sections of the Forms affected

2) A description of the outcome/resolution of any incomplete, erroneous, or altered Forms

v. For each TIRF dispense authorization (i.e., the prescriber provided documentation of opioid tolerance), provide the following:

1) The number of these prescriptions that were dispensed by the pharmacy.

2) For those prescriptions that were not dispensed, provide the reasons (e.g., patient not opioid tolerant as per the pharmacist, insurance/financial, etc.)

vi. For all dispensed TIRF prescriptions, provide an evaluation to confirm opioid tolerance based on the specific product, strength, frequency and duration provided on the Forms.

1) Conduct a quarterly analysis of patients prescribed TIRFs to assess whether they met the threshold for opioid tolerance. Provide the results of these analyses in the annual assessment reports. The performance thresholds for this analysis have been set as follows:

a) By the Year One assessment report, at least 80% of prescriptions written for TIRFs will be for opioid tolerant patients, as defined in labeling

b) By the Year Two assessment report, at least 90% of prescriptions written for TIRFs will be for opioid tolerant patients, as defined in labeling

c) By the Year Three assessment report, as well as for all subsequent assessment reports, at least 95% of prescriptions written for TIRFs will be for opioid tolerant patients, as defined in labeling

2) Provide the number of prescriptions dispensed as well as the number determined to have been dispensed to opioid non-tolerant patients.

a) Describe if any such events recurred in the same patients.

b) Conduct a follow-up in these patients for any adverse events of special interest.

Health Outcomes and/or Surrogates of Health Outcomes (data collected per reporting period)

8. Surveillance Data

a. Data from the REMS Patient Registry (REMS Data, Postmarketing Adverse Event Data): Surveillance data focused on Adverse Events of Special Interest (AESI) such as Accidental Exposure, Misuse, Abuse, Addiction, Overdose, Death, Serious Adverse Event.

i. Average number of patients for each enrolled prescriber

ii. Reports of inappropriate interchanges between TIRF products (a switch from a TIRF product to second TIRF product that is not initiated at the lowest dose when beginning the second TIRF)

iii. Number and percentage of patients experiencing an Adverse Event of Special Interest AESI

iv. The total number of AESIs reported and total number of each AESI (includes cases reported to the TIRF REMS by all sources including phone, REMS Forms, and spontaneous reports received directly by the application holders) per report source

v. Risk of each AESI, as a cumulative estimate from all patients enrolled in the new program, and stratified by:

1) REMS Assessment Period

2) Patients with and without any concomitant CNS depressant medication at enrollment, as documented on the Patient Enrollment Form

3) Patients with each specific category of concomitant CNS depressant medication at enrollment

4) Type of pain noted at enrollment: cancer pain, non-cancer pain

5) Child in the home/caregiver for small children, yes or no

vi. Summary of details of AESIs reported, and outcomes of AESIs (if known)

vii. Specifically, regarding the Patient Discontinuation Form:

1) The number of such forms submitted

2) The number reporting AESI or death

3) The reasons for discontinuation indicated

viii. The number of Targeted AESI Forms expected, the number completed, and the reasons for this discrepancy

ix. Monitor whether the percentage of patients who experience AESIs is increasing or decreasing over time

b. Surveillance data to monitor events of accidental exposure, misuse, abuse, addiction, overdose, death, and pediatric cases should also be drawn from poison control center data, including case narratives.

i. Depending on results of REMS assessment reports, additional surveillance data sources may be required

c. Healthcare data to monitor events of pediatric accidental exposure requiring medical evaluation. FDA determined that the REMS assessment must include a medical record review of drug-related hospitalizations and hospital emergency department visits. Depending on the study results, administrative claims data may be required in addition to or instead of medical records data.

d. Death certificate data to monitor drug-related deaths, especially involving pediatric subjects

e. Regarding spontaneous adverse event reports:

   i. AESI reports related to specific TIRF products will be reported to the FDA in accordance with 21 CFR 314.80.

   ii. AESI reports are to be linked to the registry and de-duplicated as is possible.

   iii. AESI reports from an inpatient setting, or outpatient reports that cannot be linked to enrolled patient data will be summarized separately.

   iv. The FAERS public dashboard is to be utilized.

   v. TIRF product application holders will retrieve AESI reports from their respective safety databases and calculate reporting rates.

   vi. Each TIRF product application holder is to submit MedWatch reports in conjunction with un-blinded line listings directly to the FDA.

Knowledge

9. Periodic Surveys of Prescribers, Pharmacists, and Patients (due with the 2-Year REMS Assessment Report and annually thereafter with each assessment report)

A Knowledge, Attitude and Behavior (KAB) Survey will be conducted with random samples of prescribers, pharmacists, and patients who have prescribed, dispensed, or received a TIRF medicine.

a. Certified Prescriber KAB surveys will assess if prescribers are educated on the following:

   i. TIRF medicines contain fentanyl. Serious, life-threatening, and/or fatal respiratory depression has occurred.

   ii. Patients must be opioid tolerant to be prescribed a TIRF Medicine.

   iii. Accidental exposure to children and others and may cause severe or fatal respiratory depression.

   iv. Prescribers must counsel their patients on the risk of misuse, abuse, addiction, and overdose.

b. Certified Outpatient Pharmacist KAB surveys will assess understanding of the following key risk messages:

i. TIRF medicines contain fentanyl. Serious life-threatening, and/or fatal respiratory depression has occurred.

ii. Patients must be opioid tolerant to be prescribed a TIRF Medicine.

iii. For each outpatient prescription, the pharmacist must obtain a prescription authorization number from the TIRF REMS Access program prior to dispensing each TIRF medicine.

iv. Accidental exposure to children and others and may cause severe or fatal respiratory depression.

c. Certified Inpatient Pharmacist KAB surveys will assess understanding of the following key risk messages:

i. TIRF medicines contain fentanyl. Serious, life-threatening, and/or fatal respiratory depression has occurred.

ii. Develop internal policies and procedures to verify opioid tolerant inpatients who require TIRF medicine while hospitalized.

d. Patient KAB surveys will assess patient understanding of the following key risk messages:

i. TIRF medicines can cause you to stop breathing which can lead to death.

ii. Accidental poisoning by a child or others could cause harm or even death.

10. Knowledge Assessments (provide for each reporting period and cumulatively)

a. The number of completed post-training knowledge assessments for healthcare providers who can prescribe and pharmacy authorized representatives including the method of completion and the number of attempts to complete.

b. A summary of the most frequently missed knowledge assessment questions.

c. A summary of potential comprehension or perception issues identified with the knowledge assessment.

11. The requirement 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 goals or such elements should be modified.

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

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

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of 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 REMS modifications*, 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 022569 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 022569 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022569/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022569/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022569/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022569/S-000/

REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

REMS REVISIONS FOR NDA 022569

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 the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and prescribing information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 LCDR Jessica Voqui, PharmD, MS; Safety Regulatory Project Manager, at 301-796-2915.

Sincerely,

{See appended electronic signature page}

LCDR Mark A. Liberatore, PharmD, RAC
Deputy Director for Safety
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- 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/

MARK A LIBERATORE
12/23/2020 04:12:25 PM