DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA ######

REMS MODIFICATION NOTIFICATION

APPLICANT NAME
ADDRESS

Attention: CONTACT NAME
TITLE

Dear CONTACT:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PROPRIETARY NAME (ESTABLISHED NAME).

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

The REMS for extended-release and long acting (ER/LA) opioid analgesic products, of which DRUG is a member, was originally approved on July 9, 2012, and the most recent REMS modification was approved on May 26, 2017. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for ER/LA Opioid Analgesics must be modified to ensure that training is made available healthcare providers involved in the treatment and monitoring of patients with pain and to implement an updated FDA Blueprint for Healthcare Provider (HCP) Education (to replace the current FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics) to ensure that the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse (see FDA Blueprint Appendix A). The updated FDA Blueprint for prescribers and other HCPs who are involved in the treatment and monitoring of patients with pain must include how to manage acute and chronic pain, along with when and how to safely integrate opioids and other pharmacological and nonpharmacological therapies in the management of pain. This modification is necessary to ensure HCPs have access to comprehensive information on how to manage pain, along with when and how to safely integrate opioid analgesics that are intended for use in an outpatient setting in the management of pain.

Additionally, in accordance with section 505-1(a)(2) of the FDCA, we have also determined that a REMS is necessary for immediate-release (IR) opioid analgesic products to ensure the benefits

of these drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

As discussed at the January 25, 2017, meeting held at FDA headquarters in Silver Spring, MD, in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs for drugs with similar, serious risks, FDA has determined that all application holders of opioid analgesics that are intended for use in an outpatient setting should work together, using the existing infrastructure of the ER/LA Opioid Analgesics REMS, to develop a shared system opioid analgesic REMS.

Your proposed modified REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that DRUG poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of DRUG. FDA has determined that DRUG is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use DRUG. FDA has also determined that DRUG is a product for which patient labeling could help prevent serious adverse events. The Medication Guide should have both common content applicable to all opioid analgesics, as well as product specific information that is necessary for safe and effective use of the drug. Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed DRUG.

In addition, under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that elements to assure safe use are necessary to mitigate the serious risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse, listed in the labeling of the drug. In addition, we have

determined that a Medication Guide and a communication plan are not sufficient to mitigate these serious risks.

Your REMS must include elements to mitigate these risks, including at least the following:

1. The applicant must ensure that training is provided to prescribers who prescribe DRUG and other healthcare providers involved in the treatment and monitoring of patients with pain. See draft FDA Blueprint Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To assure access to DRUG and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing education providers to the extent practicable.

2. The applicant must provide to health care providers involved in the treatment and monitoring of patients with pain information that those health care providers can use to educate patients in the safe use, storage, and disposal of opioids.

3. The applicant must inform prescribers and other health care providers involved in the treatment and monitoring of patients with pain (e.g., pharmacists, nurses) of the existence of the REMS and the need to successfully complete the necessary training.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be at 6 months and 1 year and then annually from the date of the approval of this REMS modification. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment.

FDA strongly recommends that applicants make provision in the shared system for joint assessments of the effectiveness of the REMS.

Because we have determined that a modified REMS as described above is necessary to ensure the benefits of ER/LA opioid analgesics that are intended for use in an outpatient setting outweigh their risks, you must submit a proposed REMS modification within 180 days of the date of this letter.

Submit the proposed modified REMS as a a Prior Approval supplement (PAS) to your NDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

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

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA ######/S-000
PROPOSED REMS MODIFICATION-AMENDMENT

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

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

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

OTHER

We will be holding a teleconference on <insert date> to provide further guidance and answer questions. It is important that you assign a representative to attend this meeting.

Note that the ER/LA Opioid Analgesics shared system REMS currently uses a Type V Drug Master File (DMF) for shared system REMS submissions. Additional information regarding the process for referencing the DMF will be provided during the teleconference referenced above.

If you have any questions, call LCDR Mark A. Liberatore, PharmD; Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Appendix A