DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

SAFETY LABELING CHANGE NOTIFICATION

APPLICANT NAME
ADDRESS

Attention: CONTACT NAME
TITLE

Dear CONTACT:

Please 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) DOSAGE FORM.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

Since DRUG was approved on DATE, FDA continues to be aware of ongoing serious safety concerns related to prescription opioid analgesic misuse, abuse, addiction, overdose, and death. The Extended Release and Long Acting (ER/LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) was required in July 2012 to ensure the benefits of prescription ER/LA opioid analgesics outweighed the risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse, and abuse with these products. In September 2017, FDA announced that immediate release (IR) opioid analgesics intended for use in outpatient settings would be subject to the same REMS requirements, because the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse are present for IR opioid analgesics as well as ER/LA opioid analgesics. The ER/LA Opioid Analgesic REMS included a 4-year training target of 192,000 prescribers completing REMS-compliant continuing education (CE) training. Based on the 60-month REMS assessment report, as of February 29, 2017, 88,316 ER/LA opioid analgesic prescribers had completed accredited REMS-compliant CE activities, representing 46% of the training target of 192,000. One likely reason the training target has not been met is lack of awareness of the REMS and the importance of completing REMS-compliant CE training. This is supported by a survey of ER/LA opioid analgesic prescribers conducted 8 months after the launch of the first REMS-compliant training, which demonstrated that 41% of prescribers surveyed were unaware of the REMS. Because ER/LA opioid analgesics represent a small proportion of the overall opioid analgesic market (of the approximately 196 million prescriptions for opioid analgesics dispensed from U.S. outpatient retail pharmacies in 2017, approximately

9% were for ER/LA formulations)[1], this suggests to us that there is likely a general lack of awareness of the REMS among all opioid analgesic prescribers. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and our September 28, 2017, letter, in which we described our determination that a REMS is necessary for opioid analgesics intended for use in an outpatient setting, we believe that the new safety information should be included in the labeling for this class of drugs as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION

BOXED WARNING

In the boxed warning title, add the following language after "ADDICTION, ABUSE, AND MISUSE": **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

In the boxed warning, add the following language after the bullet regarding addiction, abuse, and misuse:

- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.X)**

RECENT MAJOR CHANGES

Boxed Warning
Warnings and Precautions (5.X)

FULL PRESCRIBING INFORMATION: CONTENTS

Update per the changes outlined in this letter

FULL PRESCRIBING INFORMATION

BOXED WARNING

In the boxed warning title, add the following language after "ADDICTION, ABUSE, AND MISUSE": **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

In the boxed warning, add the following language after the warning regarding addiction, abuse, and misuse:

[1] Source: IQVIA™, NPA. Data extracted February 2018.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.X)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

5 WARNINGS AND PRECAUTIONS

Insert the following language after the warning regarding addiction, abuse, and misuse:

5.X Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Prescribers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCD.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted.

We have determined that an extension of the discussion period will be warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for your supplement or rebuttal statement will begin when the submission is received, and will end by September 21, 2018, unless additional discussion extensions are warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

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

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you have any questions, call LCDR Mark A. Liberatore, Pharm D, RAC; 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