DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA ######

POST-APPROVAL REMS NOTIFICATION

APPLICANT NAME
Attention: CONTACT NAME
TITLE
ADDRESS

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 TRADE NAME, IF GIVEN, (ESTABLISHED NAME) DOSAGE FORM AND STRENGTH(S).

We also refer to the stakeholder, industry, and public meetings, and Advisory Committee meeting held on February 10, March 3, May 4 and 5, May 27 and 28, 2009, and July 22 and 23, 2010, respectively, at which discussions took place concerning a risk evaluation and mitigation strategy (REMS) for the class of long-acting and extended-release opioid products. FDA has analyzed the advice and comments provided during these meetings and has determined the necessary elements of the class-wide REMS.

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

Since DRUG was approved on DATE, we have become aware of substantial numbers of postmarketing reports of abuse, misuse, addiction, and overdose resulting in fatalities associated with extended-release and/or long-acting opioid drugs. DRUG NAME is a member of this class of opioids. We consider this information to be "new safety information" as defined in section 505-1(b) of the FDCA.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for certain long-acting and extended-release opioid products, including DRUG NAME, to ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The elements of the REMS are described below.

In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class.

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 extended-release and long-acting opioids, as well as product specific information that is necessary for safe and effective use of the drug.

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

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks 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 the serious risks. Your REMS must include tools to manage these risks, including, at a minimum, the following:

1. The sponsor must ensure that training is provided to prescribers who prescribe DRUG. An outline of the content for this information is described in 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 medical education (CME) providers, to the extent practicable.

2. The sponsor must provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids. An outline of the content for this information is described in Appendix B.

3. The sponsor must inform prescribers 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 no less frequent than 6 months, 12 months, and annually after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

As required under section 505-1(g)(3)(A) of the FDCA, assessments of an approved REMS must assess the extent to which the elements to assure safe use are meeting the goals of your REMS and whether the goals or elements should be modified. Your assessment plan should include the following elements along with the methodology for each element:

1. an assessment of how many prescribers of long-acting and extended-release opioids have successfully completed the training. The assessment should specify performance goals for how many prescribers can be expected to be trained within a certain period, e.g., 50% of prescribers trained within 6 months; 70% within twelve months. We recommend that you consult with accredited CME providers to determine what can be realistically be achieved through an aggressive education program and propose goals accordingly.

2. an independent audit of the quality of the content of the educational materials used by the CME providers to provide the education. The audit should evaluate the quality of the content against the content approved by FDA as part of the REMS as well as against the Accreditation Council for Continuing Medication Education (ACCME) standards for CME.

3. an evaluation of healthcare providers' awareness and understanding of the serious risks associated with these products (for example, through surveys of healthcare providers) and specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.

4. an evaluation of patients' understanding of the serious risks of these products

5. a surveillance plan that includes monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics. Surveillance needs to include information on changes in abuse, misuse, overdose addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.

6. an evaluation of drug utilization patterns. Include methodology for monitoring patterns of prescribing to identify changes in access to these products.

7. an evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills. Provide the methodology for this analysis.

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

In accordance with section 505-1, within 120 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA. Your proposed REMS submission should

include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a model for the proposed REMS (see Appendix C).

Additionally, all relevant proposed REMS materials, including educational materials, should be appended to the proposed REMS. FDA expects that the content of the educational materials will follow the attached outline, and contain more specific content on the proposed topics than is contained in the outline. FDA will review and approve the content of the training. However, FDA understands that CME providers will take the approved content and develop specific materials for training (e.g., slides, internet-based training). Accordingly, FDA does not expect the sponsor to provide and attach to the REMS the specific materials that will be used to train prescribers.

Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include the approved documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining how the REMS will be implemented. The same supporting document may be submitted by each member of the single, shared system.

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."

For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS for NDA ######/S-###"** and all subsequent submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA ######**." If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call NAME, Regulatory Project Manager, at (301) NUMBER.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
REMS Appendices A, B, and C

APPENDIX A: CONTENT OF EDUCATION PROGRAM

The training for prescribers required by the elements to assure safe use must contain the following content:

1. General information for safe opioid prescribing
    a. Patient selection and assessment
        i. Determine goal of therapy
        ii. Assessment of the risk of abuse, including history of substance abuse and serious mental illness
        iii. When relevant, determining if patient is opioid tolerant
    b. Considerations when prescribing opioids
        i. Pharmacokinetics and potential for overdose
        ii. Addiction, abuse, and misuse
        iii. Intentional abuse by patient or household contacts
        iv. Interactions with other medications/substances
    c. Managing patients taking opioids
        i. Establishing goals for treatment and evaluating pain control
        ii. Use of Patient Provider Agreements (PPAs)
        iii. Adherence to a treatment plan
        iv. Recognizing aberrant behavior
        v. Managing adverse events
    d. Initiating and modifying dosing of opioids for chronic pain
        i. As first opioid
        ii. Converting from one opioid to another
            1. Converting from immediate-release to extended-release and long-acting products
            2. Converting from one extended-release and long-acting product to another
        iii. Titrating to effect/tolerability
        iv. How to deal with missed doses
    e. Maintenance
        i. Reassessment over time

ii. Tolerance

f. Monitoring patients for misuse and abuse

i. Utilization of prescription monitoring programs to identify potential abuse

ii. Understanding the role of drug testing

iii. Screening and referral for substance abuse treatment

g. How to discontinue opioid therapy when it is not needed any longer

2. Product Specific Information

a. Pharmacokinetic characteristics

b. Product specific toxicity

c. Requirements for opioid tolerance for certain long-acting and extended-release products

d. Individual product information modules

i. Fentanyl transdermal system

ii. Hydromorphone ER

iii. Methadone (For the treatment of moderate to severe pain not responsive to non-narcotic analgesics)

iv. Morphine ER

v. Oxycodone ER

vi. Oxymorphone ER

vii. Buprenorphine (for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time)

viii. New products

3. Patient counseling

a. Information about prescribed opioid

b. How to take opioid properly

i. Adherence to dosing regimen

ii. Risk from breaking, chewing, crushing certain products

c. Reporting adverse effects

d. Concomitant use of other CNS depressants, alcohol, or illegal drugs

e. Discontinuation of opioid

f. Risks associated with sharing, i.e., overdose prevention
g. Proper storage in the household
    i. Avoiding accidental exposure
h. Avoiding unsafe exposure by preventing theft and proper disposal
i. Purpose and content of Patient Provider Agreement

APPENDIX B: PATIENT EDUCATION

Materials to provide to patients as part of patient counseling must include:

1. How to take opioid properly
    a. Adherence to dosing regimen
    b. Risk from breaking, chewing, crushing certain products
    c. Symptoms of overdose
2. Reporting adverse effects
3. Concomitant use of other CNS depressants, alcohol, or illegal drugs
4. Discontinuation of opioid
5. Risks associated with sharing
6. Proper storage in the household
    a. Avoiding accidental exposure
7. Avoiding unsafe exposure by preventing theft and proper disposal
8. Purpose and content of Patient Treatment Agreement
9. Links to Web sites with more information about topics 1 through 8

APPENDIX C: REMS TEMPLATE

Initial REMS Approval: XX/XXXX
Most Recent Modification: XX/XXXX

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release (ER) and long-acting (LA) opioids while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

A communication plan is not required.

C. Elements To Assure Safe Use

1. The sponsor must ensure that training is provided to prescribers who prescribe DRUG. An outline of the content for this information is described in 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 medical education (CME) providers, to the extent practicable.

2. The sponsor must provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids. An outline of the content for this information is described in Appendix B.

3. The sponsor must inform prescribers of the existence of the REMS and the need to successfully complete the necessary training.

D. Implementation Plan

An implementation plan is not required.

E. Timetable for Submission of Assessments

COMPANY will submit REMS Assessments to the FDA no less frequent than 6 months, 12 months, and annually after the REMS is initially approved from the date of approval of the REMS. 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 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.