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:

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),.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

The REMS for Transmucosal Immediate Release Fentanyl (TIRF), of which TRADENAME 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.

We also refer to your REMS assessments dated December 28, 2017, and February 28, 2018.

In accordance with section 505-1(g)(4)(B) of FDCA, we have determined that the approved TIRF REMS, of which TRADENAME is a member, must be modified to ensure that the benefits of the drug outweigh the risks. This determination is 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.

The goals of the TIRF REMS access program should be modified as follows:

1. Mitigate the risk of overdose by:

    a) Requiring documentation of opioid tolerance with every TIRF prescription for outpatient use.

    b) Requiring inpatient pharmacies to verify opioid tolerance in inpatients who require TIRF medicines while hospitalized.

    c) Educating prescribers, pharmacists and patients that the safe use of TIRF medicines requires patients to be opioid-tolerant throughout treatment.

2. Mitigate the risk of accidental exposure by educating health care providers (HCPs) and patients about proper storage and disposal of TIRF medicines.

3. Assess safe use and trends in accidental exposure, misuse, abuse, addiction, and overdose by enrolling all patients who receive a TIRF medicine for outpatient use in a registry.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have determined that the existing elements to assure safe use must be modified and that additional elements to assure safe use are necessary to mitigate the risk of overdose and accidential exposure. Accordingly, we are requiring that the REMS be modified to require documentation that patients are opioid-tolerant as described in the labeling of the drug prior to dispensing a TIRF medicine. We are also requiring the addition of a patient registry. Currently available data has been insufficient to monitor the adverse events in patients treated with a TIRF medicine. We have determined that a Medication Guide and a communication plan are not sufficient to mitigate this risk.

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

- Healthcare providers who prescribe a TIRF medicine for outpatient use have particular experience or training, or are specially certified. The prescriber will be required to provide documentation of opioid tolerance concurrently with each prescription for a TIRF medicine.

- Pharmacies and practitioners that dispense a TIRF medicine are specially certified. Inpatient pharmacies will be required to develop internal policies and procedures to verify opioid tolerance in patients who require TIRF medicines while hospitalized.

- A TIRF medicine is dispensed to outpatients with evidence or other documentation of safe-use conditions, including concurrent documentation of opioid tolerance.

- Each patient prescribed a TIRF medicine for outpatient use is enrolled in a registry to monitor for serious adverse events including fatal and non-fatal overdose.

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 that pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to outpatients with documentation of the safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

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.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications in track changes.

The format for the REMS document has been updated. The new REMS document template and instructions for use can be found in the draft guidance for industry *Format and Content of a REMS Document*, available at: https://www.fda.gov/AboutFDA/Transparency/Basics/ucm325201.htm. As part of your proposed REMS modification submission you should revise the REMS document using the new template. In addition, we can assist you in converting your REMS document to the new format

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes in track changes.

Because we have determined that a modified REMS as described above is necessary to ensure the benefits of TRADENAME outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

The TIRF REMS Implementation Group (TRIG) should submit the proposed modified REMS to DMF 27320. Submit your cross-reference submission as 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 MODIFICATIONS
CROSS REFERENCE TO THE REMS DMF

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.

If you have any questions, call LCDR Mark A. Liberatore, PharmD, RAC; Associate Director for Postmarket Regulatory Science 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