DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202880/S-007

SUPPLEMENT APPROVAL

Pernix Ireland Pain Limited
c/o Pernix Therapeutics
10 North Park Place
Suite 201
Morristown, NJ 07960

Attention: Leslie Sands, MS, RAC
Senior Director of Regulatory Affairs

Dear Ms. Sands:

Please refer to your Supplemental New Drug Application (sNDA) dated October 20, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZOHYDRO ER (hydrocodone bitartrate) extended-release capsules.

We acknowledge receipt of your amendment dated April 4, 2016.

This supplemental new drug application provides for proposed modifications to the approved risk evaluation and mitigation strategy (REMS) for ZOHYDRO ER. This supplement is in response to our August 27, 2015, REMS Modification Notification letter, and our February 23, 2016, email to the REMS Program Companies (RPC) advising you that your proposed REMS modification should also include changes to the ER/LA Opioid Analgesics REMS Blueprint for Prescriber Education to incorporate product-specifc language for recently approved NDAs.

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for extended release and long-acting (ER/LA) opioid analgesics products, of which ZOHYDRO ER is a member, was originally approved on July 9, 2012, and the most recent REMS modification was approved on June 26, 2015. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of ZOHYDRO ER outweigh its risks, we determined that you were required to make the following REMS modifications:

Changes to the ER/LA Opioid Analgesics REMS Blueprint for Prescriber Education to include the following information:

1. Incorporation of information regarding the use of OxyContin in the pediatric population
2. Addition of information to the titration recommendations of OxyContin for adult patients
3. Product-specific information for a recently approved ER/LA opioid analgesic, MorphaBond (morphine sulfate extended-release) tablets
4. Product-specific information for a recently approved ER/LA opioid analgesic, Belbuca (buprenorphine) buccal film

Your proposed modified REMS, submitted on April 4, 2016, and appended to this letter, is approved.

This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments. This single shared system, known as the ER/LA Opioid Analgesics REMS Program, currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems.

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

The timetable for submission of assessments of the ER/LA Opioid Analgesic REMS Program remains unchanged.

There are no changes to the REMS assessment plan described in our June 26, 2015, letter.

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 that 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 202880 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 from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j) or to prevent application of such element under 505-1(i)(1)(B) to a drug that is subject of an ANDA. 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 202880 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 202880/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 202880/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 202880/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 202880/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 202880

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.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 Mark Liberatore, PharmD; Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUDITH A RACOOSIN
04/20/2016