DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022272/S-027

SUPPLEMENT APPROVAL

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Beth Connelly
Associate Director, Regulatory Affairs

Dear Ms. Connelly:

Please refer to your supplemental New Drug Application (sNDA) dated December 8, 2014, received December 10, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for OXYCONTIN (oxycodone hydrochloride) extended-release tablets.

We acknowledge receipt of your amendments dated April 3; May 11, 14, and 18; June 2, 3, 8, and 25; and July 13, 15 and 31, 2015.

This Prior Approval supplemental application proposes revisions to the Package Insert to include language for the use in the pediatric population and provides for updates to the approved risk evaluation and mitigation strategy (REMS) for OXYCONTIN.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the patient package insert and Medication Guide, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since OXYCONTIN was approved on April 5, 2010, we have become aware of clinical trial results in opioid-tolerant pediatric patients primarily aged 11-17. During the trial, there were two patients (an 11 year old female and a 15 year old female) with treatment-emergent clinically significant oxygen desaturations. Additionally, there were four patients in the total population (two each in the 6-11 age group and 12-17 age group) that experienced the treatment-emergent adverse event of "oxygen saturation decreased." We have also become aware of a study in the published literature describing the frequency of unintentional overdose with opioids in children covered by Tennessee Medicaid. In this study, designed to develop coding algorithms to identify

serious opioid-related adverse events in pediatric patients, 25 of the 31 cases identified by the algorithm for unintentional overdose were confirmed by medical records ((positive predictive value of 81%).[1] We have also become aware of reports of adverse events, accidental injury, accidental exposure, and medication errors, which are of particular concern for the pediatric population.[2] We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors in pediatric patients aged 17 years and younger.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following to assess these serious risks:

2923 – 1 To assess the serious risks of respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors associated with the use of OxyContin in opioid-tolerant pediatric patients aged 11-17, and to assess the serious risks of respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors associated with the use of the product in children who are either younger than the approved age range or who do not meet the labeled criteria for opioid tolerance, provide reports of all postmarket adverse events occurring in children aged 17 and younger related to respiratory depression, accidental injury, overdose, misuse, accidental exposure, and all medication errors, regardless of outcome. After three years of submitting reports, submit a comprehensive analysis of these adverse event and medication errors reports, and provide an explanation of how you have addressed them.

The timetable you submitted on July 13, 2015, states that you will conduct this reporting according to the following schedule:

Final Protocol Submission: 08/2015
Interim Report Submission: 12/2015
Interim Report Submission: 12/2016
Interim Report Submission: 12/2017
Interim Report Submission: 12/2018
Final Report Submission: 04/2019

[1] Chung CP, Callahan ST, Cooper WO, et al. Development of an algorithm to identify serious opioid toxicity in children. BMC Research Notes 2015; 8: 293.
[2] NDA 22272, Periodic Safety Update Report, June 9, 2015.

2923 - 2 Conduct a nationally representative drug utilization study of sufficient detail to characterize use of OxyContin in children aged 17 years and younger. The data from this study will provide a denominator for the risks assessed in PMR #2923-1and any future safety studies and clinical trials used to assess those risks. The following analyses should be conducted with the data collected:

1) Total number of prescriptions dispensed across all settings of care
    a. stratify by age group (0-1, 2-5, 6-10, 11-17), indication, setting of care, and prescriber specialty, and geographic location
    b. provide characteristics of dose dispensed (mean, median, range)

2) Total number of unique patients receiving dispensed prescriptions across all settings of care
    a. stratify by age group (0-1, 2-5, 6-10, 11-17), indication, setting of care, and prescriber specialty
        i. provide unique incident users every quarter-year
    b. patient demographics of users of the product
    c. clinical characteristics of users of the product (including what percentage of patients are opioid tolerant at the time they get the OxyContin prescription)

3) Duration of therapy (include definitions of allowable gaps in drug therapy in calculating duration of therapy)
    a. total and stratified by indication
    b. exploration of possible 'intermittent' use
    c. percentage of patients switching from immediate-release opioids to OxyContin
    d. percentage of patients switching from other extended-release opioids to OxyContin
    e. dose adjustments over time

The timetable you submitted on July 13, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2015
Interim Report Submission:	01/2016
Interim Report Submission:	12/2016
Interim Report Submission:	12/2017
Final Report Submission:	12/2018

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for extended release and long-acting (ER/LA) opioid analgesic products, of which OXYCONTIN 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 OXYCONTIN outweigh its risks, we determined that you were required to make the following REMS modifications:

> Changes to the ER/LA Opioid Analgesics REMS Blueprint to include the following information:
>
> - Incorporation of information regarding use of OXYCONTIN in the pediatric population
> - Addition of information to the titration recommendations for adult patients

Your proposed modified REMS, submitted on July 31, 2015, and appended to this letter, is approved.

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

This REMS uses a shared system for the elements to assure safe use and the REMS assessments. This 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.

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 of 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, proposed 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 the 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 rational 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 a REMS modification*, 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 022272 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 022272 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022272/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022272/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022272/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 022272/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 REVISION FOR NDA 022272

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Diana L. Walker, PhD, Senior Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

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

/s/

SHARON H HERTZ
08/13/2015