DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206627

NDA APPROVAL

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

Attention: Edward Liao, PharmD
US Regulatory Affairs

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) dated April 26, 2014, received April 28, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Hysingla ER (hydrocodone bitartrate) extended-release tablets, 20, 30, 40, 60, 80, 100, and 120 mg.

We acknowledge receipt of your amendments dated April 30, May 6, 9, and 21, June 3, 19, and 30, July 8 (2), 9, 16, 17, 18 (2), 23, 24, 28, and 30, August 1 (2) and 25, September 11 and 15, and October 20 (2), 21 (2), 23 (2), 28, 29, and 30 (2), 2014.

This new drug application provides for the use of Hysingla ER (hydrocodone bitartrate) extended-release tablets for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

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

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 package insert and Medication

Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 21, 2014, submission containing final printed carton and container labels.

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.

We are waiving the pediatric study requirement for ages birth to less than 7 years because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients with chronic pain in this age group is extremely small.

We are waiving the pediatric study requirement for ages 7 to less than 12 years because you have demonstrated that reasonable attempts to produce a pediatric formulation necessary for this age group have failed. As required by section 505B(a)(4)(C) of the FDCA, the documentation you have provided that details why a pediatric formulation cannot be developed will be posted on the Agency's public website.

We are deferring submission of your pediatric study for ages 12 to less than 17 years for this application because this product is ready for approval for use in adults, and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2808-1 Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of Hysingla ER in patients from ages 12 to less than 17 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Final Protocol Submission:	07/2015
Study Completion:	01/2019
Final Report Submission:	07/2019

Submit the protocol(s) to your IND 059175, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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.

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 misuse, abuse, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which Hysingla ER (hydrocodone bitartrate) is a member;

- Identify an unexpected risk of serious adverse outcome of renal failure due to chronic exposure to the low molecular weight impurities in the polyethylene oxide components of Hysingla ER; and

- Identify an unexpected risk of serious embryo-fetal developmental and/or post-natal developmental adverse events due to chronic exposure to the excipients in Hysingla ER.

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:

2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission: 11/2014
Study Completion: 01/2018
Final Report Submission: 06/2018

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 11/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by

intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 11/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-4 Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 11/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

Please note the following considerations regarding the postmarketing requirements detailed above. Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate. Because many of the risk factors for misuse, abuse, addiction, overdose, and death cannot be captured using administrative databases alone, FDA is unlikely to find adequate protocols or strategies that evaluate administrative databases only as meeting the objectives outlined above.

We acknowledge that you have already been working with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies.

FDA has determined that you are also required to conduct the following individual postmarketing studies of Hysingla ER (hydrocodone bitartrate) extended-release tablets:

2808-2 Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of Hysingla ER (hydrocodone bitartrate extended-release tablets) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Hysingla ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance, *Abuse-Deterrent*

Opioids—Evaluation and Labeling (January 2013) and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

The timetable you submitted on October 28, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 10/2015
Study Completion: 10/2019
Final Report Submission: 04/2020

2808-3 Conduct a study to identify and quantify low molecular weight impurities in the (b) (4) polyethylene oxide (PEO) products used to manufacture Hysingla ER. Submit a toxicological risk assessment for the exposure to the impurities taking into consideration the maximum theoretical daily dose of Hysingla ER.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2015

2808-4 Conduct an embryo-fetal development study in the rat model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the maximum theoretical daily dose of Hysingla ER.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 02/2016
Study Completion: 08/2016
Final Report Submission: 02/2017

2808-5 Conduct an embryo-fetal development study in the rabbit model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the maximum theoretical daily dose of Hysingla ER.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/2016
Study Completion: 12/2016
Final Report Submission: 06/2017

2808-6 Conduct a pre- and post-natal development study in the rat model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the maximum theoretical daily dose of Hysingla ER.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2016
Study Completion: 02/2017
Final Report Submission: 08/2017

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioid analgesics, of which Hysingla ER (hydrocodone bitartrate) is a member.

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

2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The timetable you submitted on October 28, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2014
Trial Completion: 08/2016
Final Report Submission: 02/2017

We acknowledge that you have already been working with the holders of other approved NDAs for ER/LA opioid analgesics on this clinical trial.

Submit the protocols to your IND 059175, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (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)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Hysingla ER to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

In accordance with section 505-1 of FDCA, 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 Hysingla ER 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 Hysingla ER. FDA has determined that Hysingla ER is a product for which patient labeling could help prevent serious adverse effects and 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 Hysingla ER. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Hysingla ER.

Pursuant to 505-1(f)(1), we have also determined that Hysingla ER can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse that are listed in the labeling. The elements to assure safe use will inform and train healthcare providers about the potential risks and the safe use of Hysingla ER.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on October 30, 3014, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Hysingla ER into interstate commerce.

Because Hysingla ER will be a member of the extended-release/long-acting (ER/LA) opioid analgesics REMS, the assessment plan will be the same assessment plan required for the other products covered by this single shared system. Because the assessments required to be submitted 6-months, 12-months, and 24-months after the approval of the ER/LA opioid analgesics REMS have been submitted, the assessment plan for Hysingla ER will align with the fourth and subsequent assessments of the ER/LA opioid analgesic REMS. Therefore, your REMS assessment plan should include, but is not limited to, the following:

Scheduled REMS Assessments

1. The fourth and subsequent REMS assessments, due July 9, 2015, and annually thereafter, should include the following information:

    a. Prescriber Letter 3: 1) number of prescriber letters electronically sent, received, undeliverable, and opened, and 2) number of prescriber letters mailed and undeliverable.

    b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training (see 1.b above).

    c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by the CE providers to provide the REMS-compliant training (see 1.c above).

    d. Evaluation of Prescriber Understanding:
        i. The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.
        ii. The results of any long-term evaluation of prescribers of ER/LA opioids who have taken ER/LA Opioid REMS-funded training to determine these

prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training.

e. Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. (See 1.d above).

f. Surveillance Results: Results of surveillance and monitoring for misuse, abuse, overdose, addiction, and death (see 1.e above).

g. Drug Utilization Patterns: An evaluation of drug utilization patterns (see 1.f above).

h. Patient Access: An evaluation of changes in patient access to ER/LA opioids.

i. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.

j. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Definitions: For purposes of these REMS assessments, the following definitions apply:

1. *REMS-compliant training*: Training will be considered "REMS-compliant training" if 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA "blueprint", 3) it includes a post-course knowledge assessment of all of the sections of the "FDA blueprint", and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.

2. *FDA Blueprint*: A document entitled, "Blueprint for Prescriber Continuing Education Programs Extended-Release and Long-Acting Opioids," approved as part of this REMS, that contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioids.

Other REMS Assessment Requirements

Under section 505-1(g)(2)(C), FDA may require the submission of a REMS assessment if FDA determines that that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug or minimize the burden on the health care delivery system of complying with the strategy.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

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 206627 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.

Prominently identify the 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:

NDA 206627 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 206627
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 206627
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. 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.

EXPIRY DATING PERIOD

A 24-month expiry dating period is granted for Hysingla ER, all dosage strengths in 60 count HPDE bottles, when stored at 20° to 25°C (68° to 77°F) with excursions permitted from 15° to 30°C (59° to 86°F).

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 Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Content of Labeling
Carton and Container 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
11/20/2014