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APPLICATION NUMBER:

22-272

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022272 **COMPLETE RESPONSE**

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

Attention: Craig Landau, M.D.
CMO & VP Clinical, Medical & Regulatory Affairs

Dear Dr. Landau:

Please refer to your new drug application (NDA) dated November 29, 2007, received November 29, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OxyContin (Oxycodone Hydrochloride Controlled-Release Tablets) 10, 15, 20, 30, 40 mg.

We acknowledge receipt of your amendments dated April 23, 2008, and March 30, May 18, June 2, 10, and 16, July 13 and 24, August 7, and September 18, October 6 and 9, November 6, 17, 19, and 23, and December 16 and 22, 2009.

The March 30, 2009, amendment constituted a complete response to our October 3, 2008, action letter, and included the addition of the 60- and 80-mg dosage strengths. However, you subsequently amended the application several times, including most recently on December 22, 2009, when you submitted a revised proposed Risk Evaluation and Mitigation Strategy (REMS).

We have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

As described in our letter dated December 11, 2009, in accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that a REMS is necessary for OxyContin to ensure that the benefits of the drug outweigh the risks of 1) use in non-opioid-tolerant individuals; 2) abuse; and 3) overdose, both accidental and intentional. We have determined that under section 505-1, the REMS for this product must include a Medication Guide and an element to assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), and a timetable for submission of assessments. FDA cannot approve your application until we have found the content of your REMS acceptable.

We acknowledge the submission of your proposed REMS on December 22, 2009. Because the REMS was submitted so late in the review cycle, FDA is deferring its review of the REMS to the next cycle.

LABELING

We reserve additional comments on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

The Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) Panel, at the joint meeting on September 24, 2009, recommended that postmarketing studies be conducted to assess whether the changes made to the OxyContin formulation that are the subject of this application and which are intended to provide deterrence of misuse and abuse actually result in a decrease in the serious risks of misuse and abuse, and their consequences: addiction, overdose and death.

FDA has determined that, if NDA 022272 is approved, you will be required to conduct postmarketing studies of OxyContin to assess the known serious risks of OxyContin, in particular, whether the changes made to the OxyContin formulation that are the subject of this application and which are intended to provide deterrence of misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences, addiction, overdose and death.

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 aforementioned risks

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

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 22272 is approved, you will be required pursuant to section 505(o)(3) of the FDCA to conduct the following:

> An epidemiological study (or studies) to address whether the changes made to the OxyContin formulation that are the subject of this application result in a decrease in misuse and abuse, and their consequences: overdose, death and addiction.

We acknowledge receipt of your proposals dated November 6 and December 16, 2009, containing your proposed brief outlines of possible postmarketing studies to fulfill this requirement. Because of design and feasibility challenges that we have noted in your proposal, we are concerned that the proposed studies will not successfully capture the necessary information that will allow us to assess the impact, if any, attributable to the change in the

OxyContin formulation. Therefore, additional information concerning the methodology and feasibility of the proposed potential studies, and possibly the addition of other studies, will be needed before agreement can be reached on the design of the postmarketing epidemiology study (or studies) that will assess the risks of reformulated OxyContin.

It will be necessary for you to complete methodology and feasibility assessments for the proposed studies. In addition, you should consider other potential outcome models for use in studying the risks associated with OxyContin, including but not limited to: accidental overdose in patients, medication errors resulting in adverse events involving the actions of healthcare providers or caregivers, unintentional overdose and/or poisoning in children, accidental overdose in recreational abusers, accidental overdose in experienced abusers, and patterns of abuse.

We will continue discussion of your postmarketing study proposals so that your complete response to this action letter contains adequately designed and acceptable studies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

We acknowledge that in a telephone conversation on December 7, 2009, you stated that you are (b) (4) We request that you submit the results of this study as soon as they become available.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

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

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