CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201655Orig1s000

OTHER ACTION LETTER(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201655

COMPLETE RESPONSE

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto
Vice President, Regulatory Affairs

Dear Mr. Barto:

Please refer to your New Drug Application (NDA) dated July 7, 2010, received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Hydrochloride Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

We acknowledge receipt of your amendments dated July 23, August 27 and 30, September 9, 14 and 29, October 1, 6, 12, 13 and 27, November 4 and 12, and December 6, 17, 27, 28 and 29, 2010, and January 3, 2011.

We also acknowledge receipt of your amendment dated January 6, 2011, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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

CLINICAL

An audit performed by the Agency of the bioequivalence study EN3288-103 identified deficiencies in the methods used at the analytical site. Because of these deficiencies, the bioequivalence study cannot be relied upon to establish bioequivalence of your proposed drug product to the reference product.

This deficiency may be addressed by doing one of the following:

1. Provided adequate samples are available, reanalyze blood samples collected in bioequivalence study EN3288-103 and submit data establishing the bioequivalence of

Oxymorphone Hydrochloride Extended-Release 40 mg tablets with OPANA ER 40 mg tablets. Ensure that the inspectional findings identified in the Agency's audit of study EN3288-103 are properly addressed in the reanalysis of blood samples.

OR

2. Conduct another pharmacokinetic study and establish the bioequivalence of Oxymorphone Hydrochloride Extended-Release 40 mg tablets with OPANA ER 40 mg tablets under fasting conditions using adequately validated analytical methodology.

OR

3. Conduct a clinical development program with clinical efficacy and safety studies to support your product.

LABELING

We reserve comment 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a 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)].

We acknowledge receipt of your proposed REMS, included in your submission dated July 7, 2010, and amended on December 17, 2010, which contains a Medication Guide, elements to assure safe use, an implementation system and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for (b) (4) (oxymorphone hydrochloride extended-release), if it is approved, to ensure that the benefits of the drug outweigh the risks of abuse, misuse, overdose and addiction. The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

As you know, we are considering what REMS elements should be implemented for a number of opioid products, including extended-release opioids to address the risks of: 1) use in non-opioid-tolerant individuals and 2) abuse, misuse, overdose, and addiction. As discussed, once that determination is made, we will notify you in writing and you will be required to submit a modified REMS incorporating those elements.

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

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. 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 E. Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

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

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