DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201655

NDA APPROVAL

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

Attention: Tara Chapman, Pharm.D.
Director, Regulatory Affairs

Dear Dr. Chapman:

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 (FDCA) for OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

We also refer to our approval letter dated December 9, 2011, which contained the following error: The statement granting an expiration dating period of (b) (4) months was incorrect.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain December 9, 2011, the date of the original approval letter.

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, 6, and 14, February 22, June 13, July 8, September 7 and 30, October 6, and November 9, 16, 21, and 30, 2011.

The June 13, 2011, submission constituted a complete response to our January 7, 2011, action letter.

This new drug application provides for the use of OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

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.

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 titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your November 9, 2011, submission containing final printed carton and container labels.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

On April 18, 2011, you were notified that in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for certain long-acting and extended-release (LA/ER) opioid products, including OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets, to ensure that the benefits of the drugs continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse, and we notified you of the elements of the REMS that would be required. You were also notified that, in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class.

While the class-wide REMS, including the single shared system, is being developed, your proposed interim REMS, submitted on November 21, 2011, and appended to this letter, is approved. This interim REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. We believe this interim REMS provides for management of the risks of adverse outcomes (addiction, unintentional overdose, and death) that is comparable to the REMS that we have determined is necessary for the class of LA/ER opioid products and is designed to ensure that the benefits of OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets continue to outweigh its risks while the single shared system, class-wide REMS is being developed.

We expect you to be working with the Industry Working Group (IWG) to develop the class-wide REMS. Prior to the implementation of the class-wide REMS, we will notify you in writing and you will be required to submit a proposed modified REMS that conforms to the class-wide REMS. The assessment plan requirements for this REMS were also described in the April 18, 2011, letter, and in that letter, FDA strongly recommended that sponsors make provision in the single shared system for joint assessments of the effectiveness of the REMS.

Your interim REMS must be fully operational before you introduce OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets into interstate commerce.

The interim REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of patients' understanding of the serious risks of OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets.

2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

4. An evaluation of healthcare providers' understanding of the serious risks of OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets

5. 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.

6. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

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.

We also 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.

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 with the following wording in bold capital letters at the top of the first page of the submission:

NDA 201655 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 201655
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 201655
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. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing,

Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

EXPIRATION DATING PERIOD

An expiration dating period of 36 months is granted for OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets, stored at 25° C (77° F) with excursions permitted from 15° to 30°C (59°-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).

In addition to the standard reporting requirements for an approved NDA, we request that you submit as 15-day expedited reports, all post-marketing and clinical trial cases of choking, gagging, sticking, and gastrointestinal obstruction, regardless of whether these reports are classified as serious or unexpected, and that you provide analyses of clinical trial and post-marketing reports of these adverse events of special interest in your periodic safety update reports.

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

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

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Build custom dashboards for your attorneys and clients with live data direct from the court.

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Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.