DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021610/S-012

SUPPLEMENT 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 Supplemental New Drug Application (sNDA) dated August 17, 2011, received August 17, 2011, submitted under section 505(b) the Federal Food, Drug, and Cosmetic Act (FDCA), for OPANA ER (oxymorphone hydrochloride) Extended-Release tablets.

We acknowledge receipt of your amendments dated March 30, and June 14 and 18, 2012.

This supplemental new drug application provides for a proposed risk evaluation and mitigation strategy (REMS) for OPANA ER (oxymorphone hydrochloride) Extended-Release tablets.

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 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 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).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your August 17, 2011, submission containing final printed carton and container labels.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS, if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements for this product were outlined in our REMS notification letter dated April 18, 2011. In that letter, 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 of extended-release or long-acting (ER/LA) opioids.

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 is appended to this letter and approved.

The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

This REMS will use a single, shared system for the elements to assure safe use and the REMS assessments. This single, shared system, known as the ER/LA Opioid REMS, currently includes the products listed in Appendix 1. Other products may be added in the future if additional NDAs or ANDAs are approved.

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.

Scheduled REMS Assessments

1. The first REMS assessment, due not later than six months from the date of REMS approval, should provide a report on the actions you have taken to implement the REMS since it was approved. The report should include the following information:

    a. Grant Proposals: The status of the requests for proposals for grants for CE training including: 1) how many have issued and when will the next requests for proposals issue; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each of the grantees will make their CE training available; 6) a high-level description of each program (e.g., web based, live); and 7) an estimate of how many prescribers are expected to be trained under each program.

    b. Evaluation Grants: The status of the requests for proposals for special grants to CE providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken training funded under this REMS to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.

    c. Functional Components:
        i. Date when the ER/LA Opioid REMS website was live and functional.
        ii. Prescriber Letter 1: 1) Date when letter was posted on the ER/LA Opioid REMS website 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.
        iii. Professional Organization/Licensing Board Letter 1: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.
        iv. Date when the single number toll free call center was operational.

2. The second REMS assessment, due one year from the date of this letter, should include the following information:

    a. Functional Components:
        i. Training: 1) Date the first REMS-compliant training was available; 2) a high-level description of the training (e.g., web based, live); 3) the number of prescribers that have undergone the training, and 4) an estimate of how many prescribers will be trained under the program(s).
        ii. Prescriber Letter 2: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received,

undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

iii. Professional Organization/Licensing Board Letter 2: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.

b. Grant Proposals: An update on the status of the requests for proposals for grants for REMS-compliant training, including: 1) new grant requests for proposals published; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each grantee will make or has made their REMS-compliant training available; 6) a high-level description of each program (e.g., web based, live), and 7) an estimate of how many prescribers will be trained under each program.

c. Evaluation Grants: The status of the requests for proposals for special grants to CE providers who also agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken their 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 including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.

3. The third REMS assessment, due two years from the date of this letter, should include the following information:

a. Prescriber Letter 3: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals, based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:

i. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained;
ii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of active prescribers) are to have been trained;
iii. Within four years from the time the first REMS- compliant training becomes available, 192,000 prescribers (based on 60% of active prescribers) are to have been trained.

c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by providers to provide the REMS-compliant training. Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) REMS-compliant training not funded under the ER/LA Opioid REMS that will be counted as REMS–compliant training for purposes of meeting the milestones in 3a., and must evaluate:
   i. whether the content of the training covers all elements of the FDA "blueprint" approved as part of the REMS;
   ii. whether the post-course knowledge assessment measures knowledge of all sections of the FDA "blueprint"; and
   iii. whether the training was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies.

d. 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. This evaluation may include, for example, surveys of patients.

e. Surveillance Results: Results of surveillance for misuse, abuse, overdose, addiction, and death. Surveillance needs to include information on changes in abuse, misuse, overdose, addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency departments, addiction treatment centers, poison control call centers). The information should be drug-specific whenever possible.

f. Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioids, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills;

g. Patient Access: An evaluation of changes in patients access to ER/LA Opioids.

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

i. 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.

4. The fourth and subsequent REMS assessments 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.

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