# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 200822

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200822

Roxane Laboratories, Inc.
Attention: Gregory M. Hicks
Associate Director, DRA and Medical Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 9, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxymorphone Hydrochloride Extended-release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

Reference is also made to your amendments dated March 10, May 27, July 13, August 6, and November 1, 2010; February 1, April 4, April 18, April 19, June 1, and August 12, 2011; April 4, June 20, June 27, and November 21, 2012; and January 11, February 7, May 14 and July 9, 2013. In addition, we acknowledge receipt of your correspondences dated February 4, and April 22, 2010; and July 3, 2013 addressing the patent issues associated with this ANDA.

We note that the formulation of the reference listed drug (RLD) upon which you have based this application, Opana Extended-release (ER) Tablets of Endo Pharmaceuticals Inc. (Endo), is no longer being marketed in the United States. Thus, Endo's Opana ER Tablets (NDA 21-610) has been moved to the Discontinued section of the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). Reference is made to the Federal Register Notice dated June 25, 2013 (Volume 78, No. 122) in which the agency announced its determination that Endo's Opana ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg (as approved under NDA 21-610) were not withdrawn from sale for reasons of safety or effectiveness. This determination allows the agency to approve ANDAs for the discontinued drug product.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Oxymorphone Hydrochloride Extended-release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the RLD, Endo's Opana ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, respectively, as approved under NDA 21-610. Your

dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The "interim" dissolution specifications are as follows:

| | |
|---|---|
| Medium: | 50 mM Phosphate Buffer, pH 4.5 |
| Volume: | 900 mL |
| Temperature: | 37°C ± 0.5°C |
| USP Apparatus: | II (Paddle) |
| Rotational Speed: | 50 rpm |
| Specifications: | Between [redacted] (b) (4) in 1 hour |
| | Between [redacted] (b) (4) n 4 hours |
| | NLT [redacted] (b) (4) n 14 hours |

These "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (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 were outlined in our REMS notification letter dated April 19, 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 the Act 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, appended to this letter, is approved. The REMS consists of a Medication Guide and elements to assure safe use.

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

Under section 505-1(g)(2)(C), FDA can require the submission of a REMS assessment if FDA determines that an assessment is needed to evaluate whether the approved REMS should be

modified or if FDA determines that there may be a cause for action by FDA under section 505(e). Additionally, the details for what should be included in any joint assessments completed under the ER/LA Opioid Analgesic REMS are listed in Appendix 1.

Prominently identify the submission containing the REMS or any REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**ANDA 200822**
**REMS ASSESSMENT**

**NEW SUPPLEMENT FOR ANDA 200822**
**PROPOSED REMS MODIFICATION**

The RLD upon which you have based your ANDA, Endo's Opana ER Tablets, is subject to periods of patent protection. The following patents and their expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

| U.S. Patent Number | Expiration Date |
|---|---|
| 5,662,933 (the '933 patent) | September 9, 2013 |
| 5,958,456 (the '456 patent) | September 9, 2013 |
| 7,276,250 (the '250 patent) | February 4, 2023 |

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Oxymorphone Hydrochloride Extended-release Tablets, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Roxane Laboratories Inc.,(Roxane) for infringement of one or more of these patents that were the subject of the paragraph IV certifications. You notified the agency that Roxane complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '456 patent was brought against Roxane in the United States District Court for the District of Delaware [Endo Pharmaceuticals, Inc. and Penwest Pharmaceutical Co. v. Roxane Laboratories Inc, Civil Action No. 2:10-cv-10-00534]. You have notified the agency that on July 3, 2013, Roxane Laboratories Inc. entered into a settlement agreement with Endo Pharmaceuticals, Inc. and Penwest Pharmaceutical Co. and the case was dismissed.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). 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 via publicly available labeling repositories.

Sincerely yours,

*{See appended electronic signature page}*

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachments: Appendix 1
REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ROBERT L WEST

07/15/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.