



ANDA 200792

Par Pharmaceutical, Inc.  
Attention: Zuriash Berhe  
Senior Associate, Regulatory Affairs  
One Ram Ridge Road  
Spring Valley, NY 10977

Dear Sir or Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 30, 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 December 1, 2009; January 6, March 19, June 1, and June 16, 2010; March 25, March 30, March 31, April 15, August 18, and November 7, 2011; March 7, March 15, April 19, June 19, September 4, September 11, September 12, October 19, and October 26, 2012; August 13, and October 24, 2013; and September 3, 2014.

The formulation of the reference listed drug (RLD) upon which you have based this ANDA, 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"). The Agency has determined 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Endo's Opana ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg (as approved under NDA 21-610) were not withdrawn from sale for reasons of safety or effectiveness (78 FR 38053; June 25, 2013). 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 reference listed drug (RLD), Opana ER as approved under Endo's 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:

The dissolution testing should be conducted in 900 mL of 0.05M Phosphate Buffer, pH 4.5 at 37°C ± 0.5°C using USP apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

1 hour (b) (4) %  
4 hours (b) (4) %  
12 hours NLT (b) (4) %

The “interim” dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement – Changes Being Effected when there are no revisions to the “interim” specifications or when 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.

The RLD upon which you have based your ANDA, Endo’s Opana ER, is subject to a period of patent protection. As noted in the Orange Book, U.S. Patent No. 7,276,250 (the ‘250 patent) will expire on February 4, 2023.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the ‘250 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Oxymorphone Hydrochloride Extended-release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, under this ANDA. You have notified the agency that Par Pharmaceutical, Inc. (Par) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Par within the statutory 45-day period.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS (REMS)**

Section 505-1 of the Act 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)].

The details of the REMS requirements were outlined in the 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 applicants of Extended-Release and Long-Acting (ER/LA) opioid analgesics.

Your proposed REMS, submitted August 18, 2011, and amended on June 19, September 11, October 19, 2012; October 24, 2013; and September 3, 2014 and appended to this letter, is approved. The REMS consists of a Medication Guide and elements to assure safe use (ETASU).

This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments are jointly completed by the ER/LA opioid analgesic applicant holders. This single, shared system, known as the ER/LA Opioid Analgesics REMS Program, currently includes the products listed on the FDA REMS website available at

<http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf>

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 an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS. The details for what should be included in any joint assessments completed under the ER/LA Opioid Analgesics REMS are listed in Appendix 1.

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.

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

**ANDA 200792  
REMS ASSESSMENT**

**NEW SUPPLEMENT FOR ANDA 200792  
PROPOSED REMS MODIFICATION**

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.

Post-marketing 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(s) 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.

You have been requested to provide information after the ANDA has been approved. Any information submitted to meet the conditions requested in this letter is considered a “Post Approval Commitment Response.” To alert the Office of Generic Drug staff to the fact that you are providing post approval commitment information, please designate your submission in your cover letter as “POST APPROVAL COMMITMENT RESPONSE.”

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.

If you have any questions, call Lyndsay Hennessey, Regulatory Project Manager, at 240-402-3746.

Sincerely yours,

Robert L.  
West -S

Digitally signed by Robert L. West -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Robert L. West -  
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For CAPT Jason J.Y. Woo, M.D., M.P.H.  
Acting Director, Office of Regulatory Operations  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Enclosures:

Appendix 1 - REMS

## Appendix 1

Because DRUG will be a member of the ER/LA opioid analgesics REMS, the assessment plan will be the same assessment plan required for the other products covered by this single shared system. Because the 6-month, 12-month, and 24-month assessments have been submitted, the assessment plan for DRUG will align with the fourth and subsequent assessments of the ER/LA opioid analgesic REMS. Therefore, your REMS assessment plan should include, but is not limited to the following:

### Scheduled REMS Assessments

1. The fourth and subsequent REMS assessments, due July 9, 2015, and annually thereafter, 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.
  - 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 became 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 became 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 became 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 the CE 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 1b, 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 Prescriber Understanding:
  - i. The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.
  - ii. The results of any long-term evaluation of prescribers of ER/LA opioids who have taken 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.
  
- e. 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.
  
- f. Surveillance Results: Results of surveillance and monitoring 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.
  
- g. 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;
  
- h. Patient Access: An evaluation of changes in patient access to ER/LA opioids.
  
- i. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.
  
- j. 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.

Definitions: For purposes of these REMS assessments, the following definitions apply:

1. *REMS-compliant training:* Training will be considered "REMS-compliant training" if 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA "blueprint", 3) it includes a post-course knowledge assessment of all of the sections of the "FDA blueprint", and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.

2. *FDA Blueprint*: A document entitled, “Blueprint for Prescriber Continuing Education Programs Extended-Release and Long-Acting Opioids,” approved as part of this REMS, that contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioids.