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RESEARCH**

APPLICATION NUMBER:

21-610

21-611

APPROVABLE LETTER

AE Letter
10/15/03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-610

Endo Pharmaceuticals Inc.
100 Painters Drive
Chadds Ford, PA 19317

Attention: MaryAlice Raudenbush, MS
Vice President, Regulatory Affairs

Dear Ms. Raudenbush:

Please refer to your new drug application (NDA) dated December 19, 2002, received December 19, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Hydrochloride Extended-Release Tablets.

We acknowledge receipt of your submissions dated January 17 and 24, February 4, 11, and 13, April 15, July 8, 17, 22, and 31, August 6, 7, 13, 14, 19, 20, 21, 27, and 29, September 3, 4, 8, 11, 12, 15, 17, and 30, 2003.

We also acknowledge receipt of your submissions dated October 6 and 8, 2003. These submissions were not reviewed for this action. You may incorporate these submissions 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 it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies.

1. An additional adequate and well-controlled trial(s) must be performed in order to provide the following information:
 - a. Efficacy over a twelve-week period in an appropriate chronic pain population in order to provide replication of the results of Study EN3202-016. This is based on the Agency's assessment of Studies EN3202-015 and EN3202-025 which did not find compelling evidence of efficacy, and Study EN3202-012 which raised safety concerns regarding the use of TRADEMARK in post-operative patients.
 - b. Safety data that will address the Agency's concerns regarding TRADEMARK'S effects on liver function, WBC count, and QTc interval.
2. Assessments of the mechanism of oxymorphone-induced positive findings in the *in vivo* micronucleus assay and their relevance to patients. Although you have hypothesized that oxymorphone produces this result in a manner similar to that reported for morphine, this

hypothesis has not been tested for oxymorphone. The Division is willing to review proposed study protocols.

3. Adequate qualification of the impurities _____ via a minimal genetic toxicology screen (one *in vitro* gene mutation and one *in vitro* chromosomal aberration assay) or reduction of the specifications for each of these impurities to NMT _____. In addition, provide a repeat-dose toxicology study of at least 14-days duration for each compound in a single species.
4. The following comments pertain to the drug substance:
 - a. The DMF 14502 for oxymorphone hydrochloride is deficient. A deficiency letter has been sent to Mallinckrodt Chemical Company, Inc., the holder of the DMF.
 - b. Information to support the stereochemical configuration and stereoisomeric purity (i.e., the synthetically introduced chiral center) of oxymorphone hydrochloride has not been provided.
 - c. Complete and detailed characterization of the crystalline form _____ and appropriate controls to ensure consistency have not been provided.
 - d. Revision of the related substance specifications to correlate with the ICH Q3A (R) recommendation as necessary as follows:
 - (1) Change the "Individual Unknown: NMT _____" to "Individual unspecified drug related impurity: NMT _____"
 - (2) Change the "Total related substances (known and unknown) NMT _____" to "Total (sum of individual reported impurities > _____)." The level should be reduced to a value based upon supporting drug substance batch data.
 - e. Control of the impurities _____ (structural alerts for mutagenicity) which are identified as impurities to levels well below (e.g., _____) the current drug substance specification of NMT _____ is necessary. Coordinate with the DMF holder, Mallinckrodt, to submit a tightened specification acceptable to the agency, or provide adequate qualification of the impurities. For _____, this qualification should include a minimal genetic toxicology screen (one *in vitro* mutagenicity assay and one *in vitro* chromosome aberrations assay) testing each compound at the limit dose for the assay. Should a genetic toxicology assay yield a positive result, the specification for the impurity should be lowered to NMT _____ or the impurity should be adequately qualified via a carcinogenicity assessment in a single species. For _____, given the positive result in the *in vitro* chromosome aberrations assay, the specification for the impurity should be lowered to NMT _____ or the impurity should be adequately qualified via a carcinogenicity assessment in a single species.
 - f. Justification with supporting data for loss on drying's acceptance criterion of NMT _____ has not been provided.

- g. A specification for the _____ in the drug substance using an accurate and specific method (e.g., Karl Fischer titration) has not been provided.
 - h. Particle size distribution of the drug substance is a critical parameter in manufacturing the drug product and has not been provided. Provide a specification for the drug substance particle size distribution. The particle size specification should include an acceptable particle size distribution in terms of particles in given size ranges, the mean particle size, and defined upper and lower particle size limits. Provide data, data analysis, and justification for the proposed specifications.
 - i. The method validation for the HPLC drug substance assay and related substances (method _____) has not been provided. In addition, the specifications should be revised to establish the chromatographic methods for assay and related substances as the "regulatory" methods for the NDA, replacing their designation as "alternate" methods.
 - j. Justify the proposed retest date _____ for oxymorphone hydrochloride supplied by Mallinckrodt.
5. The following comments pertain to the drug product:
- a. Tighter _____ specification for the TIMERx^2 -N, _____ specification should be provided. Justification should be based on the batches used in the manufacturing of the NDA exhibit batches and biobatches.
 - b. The following _____ tests should be performed on a routine basis in every commercial production of the extended-release tablets:
 - (1) The following tests on the _____ should be performed and acceptance criteria provided:

 - (2) The following _____ should be added and the following acceptance criteria provided:

 - c. The acceptance criteria for the level of degradation products and impurities in the drug product at release and on stability should be revised as follows:
 - (1) The specification for "unknown" should be revised to "any individual unspecified."
 - (2) Qualification of the impurities _____ as safe should be performed, and appropriate data submitted. Toxicological qualification should be

based upon a maximum daily dose of 1 gram. Alternatively, tighten the release and stability limit to NMT _____ for _____ these impurities.

- (3) A specification for potential _____ degradants (structural alerts for mutagenicity; see related drug substance comment) arising from the drug substance has not been provided.
 - (4) The acceptance criteria for total impurities and degradation products should be tightened and supporting data and data analysis provided.
- d. A test and an acceptance criterion for the _____ in the drug product release and stability specifications have not been included.
 - e. A revised drug product specification and stability protocol appropriately incorporating changes in response to FDA comments, e.g., degradation product specifications, _____, etc. should be included.
 - f. Based on the available stability results and statistical analysis of the stability data, the proposed expiration date of 36 months is not acceptable. Updated drug product stability data, with statistical analysis, incorporating the appropriate changes in specification in response to this letter should be provided.
 - g. Since TIMRx²-N _____ it's manufacturing site is subject to FDA inspection. Appropriately amend your NDA and confirm the address and CFN number for this manufacturing site. In addition a deficiency letter has been sent to the holder of DMF 11868 for TIMERx²-N.
6. The following comments pertain to the proposed Risk Management Plan (RMP).

We acknowledge that the risk management plan you have submitted includes educational programs directed at healthcare professionals, pharmacists, and patients and caregivers, and a plan for post-marketing surveillance. The proposed plan is deficient in that it lacks sufficient detail elaborating on these elements and lacks one of the major components of risk management programs for modified-release opioids, i.e, proposed interventions for problems detected through surveillance. We are available to work with you to improve this risk management program.

Submit revised draft labeling, including Patient Package Insert, Carton and Container Labels, incorporating changes provided in the attached marked-up labeling. Further labeling comments will be provided once the aforementioned deficiencies are adequately addressed.

Even though it is not an approvability issue, we strongly recommend that you evaluate the relative potency of oxymorphone extended-release tablets to at least one other commonly prescribed, approved modified-release opioid in an appropriate clinical setting.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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 non-clinical and clinical studies 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:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - b. Present tabulations of the new safety data combined with the original NDA data.
 - c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d. 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 study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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If you have any questions, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE

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Sharon Hertz

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Signing for Bob Rappaport, M.D.

AE Letter 10/15/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-611

Endo Pharmaceuticals Inc.
100 Painters Drive
Chadds Ford, PA 19317

Attention: MaryAlice Raudenbush, MS
Vice President, Regulatory Affairs

Dear Ms. Raudenbush:

Please refer to your new drug application (NDA) dated December 20, 2002, received December 20, 2002, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Hydrochloride Immediate-Release Tablets.

We acknowledge receipt of your submissions dated January 17 and 24, February 4, 11, and 13, April 15, July 8, 17, 22, and 31, August 6, 7, 13, 14, 19, 20, 21, 27, and 29, September 3, 4, 8, 11, 12, 15, 17, and 30, 2003.

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We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies.

1. An additional adequate and well-controlled trial is necessary in order to provide the following information:
 - a. The safe and effective use of TRADEMARK in an appropriate opioid-naïve population that includes data on multiple dosing.
 - b. The safe use of TRADEMARK in the postoperative setting or other appropriate clinical setting.
 - c. A safe and effective dosing interval.
 - d. A complete assessment of the abnormalities in liver function tests, WBC count, and QTc interval that were documented in your completed clinical studies.
2. Assessments of the mechanism of oxymorphone-induced positive findings in the *in vivo* micronucleus assay and their relevance to patients. Although you have hypothesized that

oxymorphone produces this result in a manner similar to that reported for morphine, this hypothesis has not been tested for oxymorphone. The Division is willing to review proposed study protocols.

3. Adequate qualification of the impurities _____ via a minimal genetic toxicology screen (one *in vitro* gene mutation and one *in vitro* chromosomal aberration assay) or reduction of the specifications for each of these impurities to NMT _____. In addition, provide a repeat-dose toxicology study of at least 14-days duration for each compound in a single species.
4. The following comments pertain to the drug substance:
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 - b. Information to support the stereochemical configuration and stereoisomeric purity (i.e., the synthetically introduced chiral center) of oxymorphone hydrochloride has not been provided.
 - c. Complete and detailed characterization of the crystalline form _____ and appropriate controls to ensure consistency have not been provided.
 - d. Revision of the related substance specifications to correlate with the ICH Q3A (R) recommendation is necessary as follows:
 - (1) Change the "Individual Unknown: NMT _____" to "Individual unspecified drug related impurity: NMT _____"
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- j. Justification for the proposed retest date _____ for oxymorphone hydrochloride supplied by Mallinckrodt has not been provided.

5. The following comments pertain to the drug product:

- a. Appropriately tight specifications for particle size distribution of the excipients (_____)

- b. An appropriately detailed description of the manufacturing process has not been provided.

- c. The proposed drug product is noted to have a narrow therapeutic range, is manufactured through a _____ process, and has a relatively low percentage of the drug substance in its composition. The following concerns derive from these characteristics:

- d. The following comments pertain to degradant impurities in the drug product:
- (1) The specification for “unknown” impurity should be revised to “any individual unspecified” impurity.
 - (2) Qualification of the impurities _____ as safe should be performed, and appropriate data submitted. Toxicological qualification should be based upon a maximum daily dose of 1 gram. Alternatively, tighten the release and stability specified limit to NMT _____ for _____ these impurities.
 - (3) A specification for potential _____ degradants (structural alerts for mutagenicity; see related drug substance comment) arising from the drug substance has not been provided.
 - (4) The acceptance criteria for total degradation products should be tightened and supporting data and data analysis provided.
- e. The acceptance criteria in the specification for dissolution (e.g., to $Q = \text{---}$ at 10 minutes in 0.1 N HCl) should be tightened.
- f. A revised drug product specification and stability protocol appropriately incorporating changes in response to FDA comments, e.g. degradation product specifications and dissolution specifications should be provided.
- g. FDA analysis of the currently submitted 24-month stability data indicate a 30-month expiry dating period. Updated drug product stability data, with statistical analysis, incorporating the appropriate changes in specifications in response to this letter should be provided.

Submit revised draft labeling, including Carton and Container Labels, incorporating changes provided in the attached marked-up labeling. Further labeling comments will be provided once the aforementioned deficiencies are adequately addressed.

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3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
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Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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/s/

Bob Rappaport
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