

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-610

21-611

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PATENT INFORMATION and EXCLUSIVITY
Oxymorphone ER – EN3202

DATE: 17 December 2002

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

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that is privileged or confidential and may not be disclosed to third parties, unless such disclosure is required by law or used for any purpose, without the prior written consent of Endo. In any event, persons to whom the information is disclosed upon the written consent of Endo must be informed that the information is privileged or confidential and may not be further disclosed by them or used for any purpose. These restrictions on disclosure will apply equally to all future information supplied to you and which is indicated as privileged or confidential

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ATTACHMENT 1

Patent/Exclusivity Information

- | | | |
|-----|--|---|
| 1) | Active Ingredient(s) | <u>Oxymorphone HCl</u> |
| 2) | Strength(s) | <u>5 mg, 10 mg, 20 mg and 40 mg</u> |
| 3) | Trade Name | <u>N/A</u> |
| 4) | Dosage Form
(Route of Administration) | <u>Tablets</u> |
| 5) | Application Form Name | <u>Endo Pharmaceuticals Inc.</u> |
| 6) | IND Number | <u>56,919</u> |
| 7) | NDA Number | <u>21-610</u> |
| 8) | Exclusivity* - Length of
exclusivity period | <u>3 years from final approval</u> |
| 9) | Applicable patent numbers
and expiration date of each | <u>4,994,276 Exp. 9/19/08</u>
<u>5,128,143 Exp. 9/19/08</u>
<u>5,554,387 Exp. 9/10/13</u> |
| 10) | Endo claims a period of marketing exclusivity pursuant to 21 CFR 314.108(b)(4). We certify that, to the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a). Endo was the sponsor named in investigational new drug application (IND) number 56,919, under which the clinical investigations essential to approval of this application were conducted. | |

A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which we are seeking approval is available upon request. We certify that we have thoroughly searched the scientific literature and, to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which we are seeking approval without reference to the new clinical investigation(s) in the application.

* Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) of the Federal Food, Drug and Cosmetic Act, no ANDA or 505(b)(2) NDA may be approved with an effective date which is prior to 3 years (5 years for NCE) after the date of approval of this application.

ATTACHMENT 2.

Item 13. Patent Information

- | | |
|-------------------------|------------------------------------|
| 1) Patent number | <u>4,994,276</u> |
| 2) Date of expiration | <u>September 19, 2008</u> |
| 3) Type of patent | <u>Utility</u> |
| 4) Name of patent owner | <u>Penwest Pharmaceuticals Co.</u> |
| 5) U.S. representative | <u>Hale and Dorr LLP</u> |

The undersigned declares that Patent No. 4,994,276 covers the formulation, composition, and/or method of use of Oxymorphone ER. This product is the subject of this application for which approval is being sought.

signed: Hale and Dorr, agent for Penwest Pharmaceuticals Co.

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ATTACHMENT 2.

Item 13. Patent Information

- | | |
|-------------------------|------------------------------------|
| 1) Patent number | <u>5,128,143</u> |
| 2) Date of expiration | <u>September 19, 2008</u> |
| 3) Type of patent | <u>Utility</u> |
| 4) Name of patent owner | <u>Penwest Pharmaceuticals Co.</u> |
| 5) U.S. representative | <u>Hale and Dorr LLP</u> |

The undersigned declares that Patent No. 5,128,143 covers the formulation, composition, and/or method of use of Oxymorphone ER. This product is the subject of this application for which approval is being sought.

signed:

Hale and Dorr LLP, agent for Penwest Pharmaceuticals Co.

Appears This Way
On Original

ATTACHMENT 2.

Item 13. Patent Information

- | | |
|-------------------------|------------------------------------|
| 1) Patent number | <u>5,554,387</u> |
| 2) Date of expiration | <u>September 10, 2013</u> |
| 3) Type of patent | <u>Utility</u> |
| 4) Name of patent owner | <u>Penwest Pharmaceuticals Co.</u> |
| 5) U.S. representative | <u>Hale and Dorr LLP</u> |

The undersigned declares that Patent No. 5,554,387 covers the formulation, composition, and/or method of use of Oxymorphone ER. This product is the subject of this application for which approval is being sought.

signed: Hale and Dorr LLP agent for Penwest Pharmaceuticals Co

Appears This Way
On Original

ATTACHMENT 1

Patent/Exclusivity Information

- | | | |
|----|--|------------------------------------|
| 1) | Active Ingredient(s) | <u>Oxymorphone HCl</u> |
| 2) | Strength(s) | <u>5 mg and 10 mg</u> |
| 3) | Trade Name | <u>N/A</u> |
| 4) | Dosage Form
(Route of Administration) | <u>Tablets</u> |
| 5) | Application Form Name | <u>Endo Pharmaceuticals Inc.</u> |
| 6) | IND Number | <u>58,602</u> |
| 7) | NDA Number | <u>21-611</u> |
| 8) | Exclusivity* - Length of
exclusivity period | <u>3 years from final approval</u> |
| 9) | Applicable patent numbers
and expiration date of each | <u>N/A</u> |

- 10) Endo claims a period of marketing exclusivity pursuant to 21 CFR 314.108(b)(4). We certify that, to the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a). Endo was the sponsor named in investigational new drug application (IND) number 58,602, under which the clinical investigations essential to approval of this application were conducted.

A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which we are seeking approval is available upon request. We certify that we have thoroughly searched the scientific literature and, to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which we are seeking approval without reference to the new clinical investigation(s) in the application.

* Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) of the Federal Food, Drug and Cosmetic Act, no ANDA or 505(b)(2) NDA may be approved with an effective date which is prior to 3 years (5 years for NCE) after the date of approval of this application.

EXCLUSIVITY SUMMARY

NDA # 21-610

SUPPL #

HFD # 170

Trade Name OPANA ER

Generic Name (oxymorphone hydrochloride extended-release) Tablets

Applicant Name Endo Pharmaceuticals

Approval Date, If Known 6/22/06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

EN3202-031

EN3202-032

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study # EN3202-031

Study # EN3202-032

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 56,919 YES ! NO
! Explain:

Investigation #2
IND # 56,919 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Lisa Basham

Title: Regulatory Project Manager

Date: 6-21-06

Name of Office/Division Director signing form: Sharon Hertz, MD (for Bob Rappaport, MD)

Title: Deputy Director, DAARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Bob Rappaport
6/22/2006 07:01:44 PM

EXCLUSIVITY SUMMARY

NDA # 21-611

SUPPL #

HFD # 170

Trade Name OPANA (oxymorphone hydrochloride) Tablets

Generic Name oxymorphone hydrochloride

Applicant Name Endo Pharmaceuticals

Approval Date, If Known 6/22/06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 11-707 oxymorphone hydrochloride Injection 1 mg/mL

NDA# 11-738 oxymorphone hydrochloride rectal suppositories

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

EN3203-009
EN3203-004
EN3203-005

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	NO	

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
------------------	------------------------------	--

Investigation #2 YES NO

Investigation #3 NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

EN3202-009, EN3202-004, EN3202-005

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 58,602 YES ! NO
! Explain:

Investigation #2
IND # 58-602 YES ! NO
! Explain:

Investigation #3 YES

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
6/22/2006 06:58:08 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21,610 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 12/19/02 Action Date: _____

HFD 170 Trade and generic names/dosage form: OPANA (Oxymorphone Hydrochloride) Extended-Release Tablets, 5 mg, 10 mg, 20 mg, 40 mg.

Applicant: Endo Pharmaceuticals, Inc. Therapeutic Class: _____

Indication(s) previously approved: _____

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

X No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): June 30, 2011

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-610
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Bob Rappaport
6/22/2006 06:50:03 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21,611 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: 12/20/02 Action Date:

HFD 170 Trade and generic names/dosage form: OPANA (Oxymorphone Hydrochloride) Tablets, 5 mg, 10 mg

Applicant: Endo Pharmaceuticals, Inc. Therapeutic Class:

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: relief of moderate to severe acute pain where the use of an opioid is appropriate.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): June 30, 2006

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-611
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Bob Rappaport
6/22/2006 06:53:18 PM

DEBARMENT CERTIFICATION
Oxymorphone ER- EN3202

DATE: 14 December 2002

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

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that is privileged or confidential and may not be disclosed to third parties, unless such disclosure is required by law or used for any purpose, without the prior written consent of Endo. In any event, persons to whom the information is disclosed upon the written consent of Endo must be informed that the information is privileged or confidential and may not be further disclosed by them or used for any purpose. These restrictions on disclosure will apply equally to all future information supplied to you and which is indicated as privileged or confidential

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**EN3202 (oxymorphone hydrochloride)
Extended-Release Tablets**

DEBARMENT CERTIFICATION

In accordance with the requirement of section 306(k) of the Federal Food, Drug, and Cosmetic Act, I certify that Endo Pharmaceuticals Inc. did not use and will not use in any capacity in connection with this application the services of any person debarred under subsections (a) or (b) of sections 306(k).



Mary Alice Raudenbush, M.S.
Vice President, Regulatory Affairs

On this 17 day of January 2003

Privileged and Confidential

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

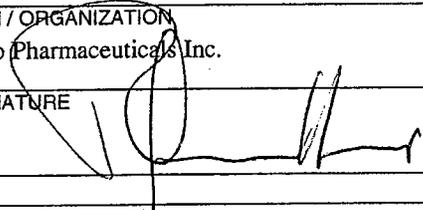
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Roland Gerritsen van der Hoop		TITLE Senior Vice President, Research & Development and Regulatory Affairs	
FIRM / ORGANIZATION Endo Pharmaceuticals Inc.			
SIGNATURE 		DATE 10/24/05	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

2nd Cycle
Review

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 19, 2006

TO: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170

THROUGH: Jonca Bull, M.D., Acting Deputy Director
Office of Surveillance and Epidemiology

FROM: ODS Oxymorphone RiskMAP Review Team

DRUG: Opana IR/ER (Oxymorphone Hydrochloride) NDA #21-611, 21-610

APPLICANT: Endo Pharmaceuticals

SUBJECT: Review of Risk Minimization Action Plan, submitted December 22, 2005

PID: D060231

1 EXECUTIVE SUMMARY

This consult follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Risk Minimization Action Plan (RiskMAP) for Oxymorphone oral dosage forms, an immediate-release (IR) tablet (NDA 21-611) and an extended-release (ER) tablet (NDA 21-610), submitted by Endo Pharmaceuticals on August 31, 2005.

In general, we agree with the Sponsor's RiskMAP approach that includes proposed labeling, a plan to educate HCPs and patients about the risks associated with oxymorphone, and a pharmacovigilance plan.

OSE considers the greatest risk to be with the ER form of oxymorphone, rather than the IR form and we note that the Sponsor has submitted one RiskMAP that applies to both oral formulations. We believe that ER opioid products, when used inappropriately (e.g., chewed, crushed, etc), may incur a greater risk of respiratory depression, particularly at the higher doses. Therefore, OSE recommends that the major focus of the RiskMAP for oxymorphone should be to educate patients and HCPs on the appropriate use of oxymorphone ER as well as the differences between the IR formulation of oxymorphone and the ER form.

OSE has some concerns about the ER oxymorphone tablets, in addition to our comments on the RiskMAP. OSE is also concerned that the current proposed product label does not specifically address whether the higher doses of oxymorphone ER can be used in opioid-naïve patients which differs from the labeling in the oxycodone labeling and higher doses.

The Sponsor has addressed and resolved a number of OSE preliminary concerns and comments regarding the RiskMAP for Opana and Opana ER. Remaining concerns and recommendations are discussed in Section 6 of this document and in a DMETS Pre-Marketing Consult signed June 12, 2006 in DFS.

2 BACKGROUND/PRODUCT INFORMATION¹

Oxymorphone (14-hydroxydihydro-morphinone) is a semi-synthetic opioid analgesic that is structurally related to morphine and is a metabolite of oxycodone. The drug was first approved in 1959 and an immediate release (IR) oral form was marketed in the early 1960s. The IR form was voluntarily removed from the market for “commercial” reasons in the 1970s (the 2 mg and 5 mg tablets were removed after 7 years of marketing and the 10 mg tablet was removed after 11 years).² Endo currently has approval for an injectable (NDA 11-707) and rectal suppository dosage forms of oxymorphone (NDA 11-738, discontinued marketing in 2004).

OPANA (oxymorphone hydrochloride) IR is supplied in 5 mg and 10 mg tablet strengths for oral administration with a proposed indication of relief of moderate to severe pain where the use of an opioid is appropriate. Patients who have not been receiving opioid analgesics should be started on OPANA in a dosing range of 10 to 20 mg depending on the initial pain intensity given every 4 to 6 hours prn. If deemed necessary to initiate therapy at a lower dose, patients may be started with OPANA 5 mg and may be dosed as frequently as every 2 hours.

OPANATM ER (oxymorphone hydrochloride) is supplied in 5 mg, 10 mg, 20mg, and 40 mg tablet strengths for oral administration with a proposed indication of management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed. OPANATM ER is not intended for use as a prn analgesic. The proprietary extended-release technology (TIMERx[®]-N) employed in formulation of OPANATM ER allows it to be effectively administered every 12 hours.

OPANA immediate-release tablets proposed indication is for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OPANA ER is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate or severe and persist for an extended period of time. It is suggested that patients who are not opioid-experienced being initiated on chronic around-the-clock opioid therapy be started with OPANA ER 5 mg q12h. Patients receiving OPANA IR may be converted to OPANA ER by administering half the patient's total daily oral OPANA IR dose as OPANA ER, q12 hours. For example, a patient receiving 40 mg/day OPANA IR may require 20 mg OPANA ER q12h.

¹ Proposed Label for NDA 21-610 and 21-611: Oxymorphone Hydrochloride and Oxymorphone Hydrochloride Extended-Release Tablets; submitted 3-22-06.

² ODS Review: Review of Oxymorphone HCL CR and IR Risk Management Plan. June 19, 2003, PID#: D030188

3 SUMMARY OF SPONSOR'S RISK MANAGEMENT PROPOSAL

The Sponsor's submission contains proposed labeling, an education-based RiskMAP including patient education (including Pain Control Initiatives) and education for Health Care Providers, and Sales Force Training, as well as a Pharmacovigilance Plan.

The Sponsor's goals and objectives for this RiskMAP are to minimize the following liabilities with opioid class of drugs as it pertains to oxymorphone.

- Aberrant behavior such as drug abuse, misuse and addiction
 - among patients
 - in the community, particularly among young adults
- Unintentional drug overdose
- Accidental exposure
- Diversion from distribution/manufacturing facilities
- Improper patient selection
- Fraudulent prescription activity
- Inadequate patient education

3.1 PROPOSED LABELING

The Sponsor is proposing the following boxed warning for the ER formulation as worded in the FDA approvable letter dated October 15, 2003.

WARNING:

OPANA ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OPANA ER is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

OPANA ER is NOT intended for use as a prn analgesic.

OPANA ER TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, DISSOLVED, OR CRUSHED. TAKING BROKEN, CHEWED, DISSOLVED, OR CRUSHED OPANA ER TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYMORPHONE.

3.2 TARGETED EDUCATION AND OUTREACH

The Sponsor plans a targeted education and outreach program directed at patients, physicians, nurses, and pharmacists on the appropriate use of opioid analgesics with a particular emphasis on modified-release opioids. Endo sponsors these initiatives through unrestricted educational grants.

3.2.1 Healthcare Professional Education

- CME programs as part of the Sponsor's National Initiative on Pain Control (NIPC) – this includes a number of programs and educational materials on pain management. The intended audience includes 60,000 internists, family physicians, osteopathic medicine specialists, general neurologists, physical medicine and rehabilitation specialists, and other clinicians who manage patients with chronic pain.
- National CME-accredited initiatives presented by the Office of Women's Health.
- Satellite symposia and educational programs done in conjunction with professional organizations
- Educational program for physicians-in-training and primary care physicians on appropriate pain assessment supported through unrestricted grants from Endo
- Reference books which the Sponsor has supported by unrestricted grants from Endo

3.2.2 Patient Education

- Patient and Family Brochure' "Understanding Your Pain: Taking Oral Opioid Analgesics" – this brochure is intended to be provided to physicians and pharmacists for their patients being considered for or currently taking oral opioid analgesic therapy.
- Pain Assessment Inventory and Patient/Family Education Materials – this includes tear pads, which include the Brief Pain Inventory (BPI) and accompanying educational information on pain and pain assessment to physicians for their use in education patients
- Pain Action – Inflexxion, with support from Endo, launched PainAction.com. The Sponsor states that this consumer-oriented website provides patients and families with ways to cope with pain-related problems.

3.2.3 Additional Tools

- Tamper resistant prescription pads – The Sponsor plans to provide tamper resistant prescription tear pads to prescribers free of charge to help prevent diversion.
- Sales Force training and monitoring for compliance with training – The Sponsor states that they will monitor the compliance of sales representatives with approved marketing and sales guidelines. If needed, the Sponsor can make adjustments to its sales training curriculum to diminish the likelihood of promotional message misinterpretation.
- Oversight of the Distribution Chain – The Sponsor plans to closely monitor its manufacturing and distribution chain. The Sponsor states that their monitoring activities meet or exceed DEA requirements for CII materials.
- SOAPP (Screener and Opiate Assessment for Patients with Pain – The Sponsor is supporting development of a prospective, patient self-report screening tool being developed by NIDA. The tool screens certain patients that need extra monitoring to prevent problems with misuse.

4 SPONSOR'S PROPOSED PHARMACOVIGILANCE

The Sponsor's post marketing surveillance includes:

- TESS – planning on reviewing case reports identified in annual report
- DAWN – planning on reviewing published reports
- National Addictions Vigilance Intervention & Prevention Program (NAVIPPRO) (in development) a national drug monitoring system for prescription and non-prescription drugs of abuse by using substance abuse treatment centers
- Media screening service; looking for mentions on abuse-related websites
- IMS Health Xponent database – will be used to identify prescribing trends. The metrics used include dispensed prescriptions with specialty physician details and ZIP code geographic detail.
- Two prevention programs designed to impact teens and young adults.
- All serious adverse events and quarterly Periodic Reports will be submitted to FDA according to Federal Regulations.

5 SPONSOR'S EVALUATION PLAN

The Sponsor's proposed RiskMAP evaluation includes:

- a. Safety Review Board (ESRB) to review adverse events and identify new safety signals and trends for all Endo products. The ESRB consists solely of Endo employees. It is an internal safety surveillance process.
- b. Risk Management Team to evaluate data collected from post-marketing surveillance and secondary databases, media screening, and IMS data in order to assess the risks
- c. Risk intervention plans focus on minimizing diversion, misuse, and abuse.
- d. Endo will submit a RiskMAP progress semi-annual report.

6 OSE CONCERNS, COMMENTS, AND RECOMMENDATIONS

In general, we agree with the Sponsor's RiskMAP approach that includes proposed labeling, a plan to educate HCPs and patients about the risks associated with oxymorphone, and a pharmacovigilance plan.

OSE considers the greatest risk to be with the extended-release form of oxymorphone, rather than the immediate-release form. We believe that extended release opioid products, when used inappropriately (e.g., chewed, crushed, etc), may incur a greater risk of respiratory depression, particularly at the higher doses. Therefore, OSE recommends that the major focus of the RiskMAP for oxymorphone should be to educate patients and HCPs on the appropriate use of oxymorphone ER as well as the differences between the immediate-release formulation of oxymorphone and the extended-release form. The Sponsor's educational plan is comprehensive about the treatment of pain and general, appropriate opioid usage, but does not emphasize the potential risks associated with oxymorphone extended-release tablets.

OSE has some concerns about the extended-release oxymorphone tablets, in addition to our comments on the RiskMAP. In the proposed RiskMAP, labeling, and Endo's submission dated

May 26, 2006, the Sponsor proposes the use “IR” or “immediate-release” in conjunction with the established name to identify the immediate release dosage formulation of oxymorphone hydrochloride tablets. The use of abbreviations should be avoided in the label and educational materials in order to avoid confusion or misinterpretation with other currently used modifiers or suffixes, such as extended-release. Additionally, all dosage formulations are considered immediate release unless otherwise designated in the name. Thus, the established name for the immediate-release should be referred to as “Oxymorphone Tablets.”

Secondly, due to variance in *in vivo* and *in vitro* alcohol testing with oxymorphone ER, the labeling should carry a strong warning to avoid alcohol while taking this medication. This warning should also be reiterated in the *Dosage and Administration* section of the Package Insert. (Please refer to DMETS Pre-Marketing Consult signed June 12, 2006 in DFS). Thirdly, Endo’s May 26, 2006 submission included pictures of tablet colors for the strengths of the ER tablets. The 10 mg and 40 mg oxymorphone ER tablets, though stamped with the strength, are a similar color of yellow. We recommend that one of these strengths be changed to avoid a medication error. (Refer to DMETS Pre-Marketing Consult signed June 12, 2006 in DFS, for elaboration on these concerns.)

OSE notes that the product label does not address whether the higher doses of oxymorphone ER can be used in opioid-naïve patients. The Oxycontin label includes the following warning against use of the higher doses in opioid-naïve patients.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

However, the highest strengths of oxymorphone ER, 20 mg and 40 mg, are not as likely to cause adverse effects in opioid-naïve patients, compared to the much higher doses of OxyContin 80 mg and 160 mg.

The Sponsor has addressed and resolved a number of OSE preliminary concerns and comments regarding the RiskMAP for Opana and Opana ER. Please refer to Appendix 1 and to the response by Endo in the EDR at \\Cdsesub1\n21610\N_000\2006-05-26A\other. Additionally, OSE has the following recommendations:

Education

1. In the May 26, 2006, response, Sponsor submitted substantial educational objectives for professionals and third party initiatives. We remind Endo that although the objectives are adequate for accomplishing goals of the RiskMAP, the mechanism of unrestricted educational grants does not allow Endo to greatly influence the objectives of educational programs since they are funding them.
2. OSE and Endo have communicated about the evaluation of their educational messages. OSE finds most of the May 26, 2006 response by Endo adequate, but requests that the specific methodology and questions for direct market research with patients to evaluate their knowledge of risk be submitted for review.

Post-Marketing Reporting

Endo indicates in the RiskMAP that they will report all serious adverse events in accordance with the current Federal Regulations.

- Additionally, we request that the Sponsor submit the following as Postmarketing 15-day Alert Reports:
 - Any report in a child or adolescent (ages 0-16), whether or not the exposure was intended or unintended, and regardless of outcome.
 - Any medication error reports regardless of patient outcome
- The Sponsor mentions that the Periodic Reports will specifically be reviewed by the Endo's Safety Review Board for increased reports of abuse, misuse, or overdose. They should also include a special section in the descriptive portion of their quarterly Periodic Reports describing the status of any efforts and data relating to their risk management plan. This section should include (but not be limited to) available data on the following:
 - Extent of use (denominator estimates)
 - Indicators of off-label use or inappropriate prescribing (i.e. opioid-naive)
 - Summary of reports involving medication errors and inadvertent pediatric exposures
 - Summary of adverse events involving opioid naïve patients
 - Results of any investigation or surveys conducted
 - Outcome of any interventions, such as targeted educational interventions and antidiversion programs conducted.

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ODS Oxymorphone RiskMAP Review Team

Gita Akhavan-Toyserkani, Pharm.D., Safety Evaluator, DDRE
Boris R. Aponte, MPHE, PhD, Health Education Specialist, DSRCS
Nancy Clark, Pharm.D., Project Manager, DSRCS
Mary Dempsey, Project Management Officer, OSE IO
Jodi Duckhorn, MA, Patient Information Team Leader, DSRCS
Felicia Duffy, RN, Safety Evaluator, DMETS
Cathy Dormitzer, Ph.D., Epidemiologist, DDRE
Lauren Lee, Pharm.D., Safety Evaluator Team Leader, DDRE
Claudia Karwoski, PharmD, Scientific Coordinator, OSE IO
Alina Mahmud, RPh, MS, Team Leader, DMETS
Toni Piazza-Hepp, Pharm.D., Deputy Director, DSRCS
Mary Willy, Ph.D., Epidemiology Team Leader, DDRE

Appendix 1

Oxymorphone NDA 21-610, 21-611 RMP OSE interim comments emailed to Sponsor 5/11/06

1. Although there are objectives for the Risk Management Plan (RMP) listed, Sponsor does not appear to have identified specific safety risks pertaining to the oxymorphone extended release (ER) formulation.

- Identify any safety risks that are unique to oxymorphone ER.

OSE response to Endo's 5/26/06 response: FDA acknowledges.

Educational Plan

2. Sponsor's educational plan describes general pain management rather than oxymorphone-specific education. We acknowledge that the unrestricted grant mechanism for CME-accredited programs will limit Sponsor influence on the content.

- Develop educational tools that stress the 11 "elements" listed in Section 3.2.

OSE response to Endo's 5/26/06 response: Sponsor's response is adequate. However, we remind Endo again that by providing education through the unrestricted grant mechanism, Endo will not be able to influence the objectives of the educational program.

- Since oxymorphone immediate release (IR) and ER will be launched at the same time, develop education that emphasizes the different target populations and product specific safety issues distinguishing the two dosage forms.

OSE response to Endo's 5/26/06 response: DMETS notes that the immediate-release formulation is referred to as "IR" throughout the document. DMETS does not recommend the use of the suffix "IR" (or "immediate-release) in conjunction with the established name to identify the immediate release dosage formulation of oxymorphone hydrochloride tablets. The use of abbreviations should be avoided when possible in order to avoid confusion or misinterpretation with other currently used modifiers or suffixes. Specifically, DMETS is concerned that prescriptions will be written with the modifier "IR" which may be confused with the "ER" dosage formulation. Additionally, DMETS is concerned that sales representatives will refer to the immediate-release as "IR" thus leading practitioners to prescribe this medication using this abbreviation. All dosage formulations are considered immediate-release unless otherwise designated in the name. Thus, the established name for the immediate-release product should be referred to as "Oxymorphone Tablets."

3. Sponsor's RMP lacks a description of planned evaluation of the educational plan.

- Consider employing methods to ensure the education plan is effective so that safety messages are comprehended.

OSE response to Endo's 5/26/06 response: Endo's review of effectiveness of education for the sales force is adequate. We note that the evaluation of HCPs could show bias in that HCPs that have prescribed oxymorphone but have not been detailed by the sales force will not be evaluated. Also, send in data evaluation criteria for HCPs and more detail about the Standard Report Contents when they are available. Again, we remind you that the unrestricted grant mechanism does not allow you to "stress the need for formal evaluation of the educational initiatives" for third party educational initiatives. Lastly, for patient

evaluation of comprehension, describe what questions will be asked and the methodology used during direct market research.

4. Appendix 1 outlines Sales Force training.

- Incorporate key safety messages, such as in the boxed warning, misuse and diversion potential, and the different target formulations for the IR and ER formulations.

OSE response to Endo's 5/26/06 response: Sponsor's response is adequate.

5. Provide the 5 items listed in the Provider Toolkit in Appendix 1 when available.

OSE response to Endo's 5/26/06 response: Sponsor's response is adequate.

Surveillance

6. State the how frequently surveillance databases (DAWN, TESS, etc.) will be monitored and reported to FDA. We recommend that Endo obtain DAWN data on oxymorphone and opioid comparators directly from SAMHSA instead of waiting for biannual published reports.

OSE response to Endo's 5/26/06 response: Sponsor's response is adequate.

7. Section 3.5.2.4 of the RMP suggests using _____ Proportion Analysis Engine to compare oxymorphone ER to an unexpected value derived from a background set of drugs.

- Explain how the unexpected value is derived and at what level Endo considers the value unexpected.

OSE response to Endo's 5/26/06 response: Sponsor's response is adequate.

8. Describe how collected geographic information will used.

OSE response to Endo's 5/26/06 response: Sponsor's response is adequate.

9. Provide details and monitoring frequency for the media screening service which detects lay press articles pertaining to oxymorphone IR or ER abuse.

OSE response to Endo's 5/26/06 response: Sponsor's response is adequate.

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this page is the manifestation of the electronic signature.**

/s/

Nancy Clark
6/19/2006 02:58:02 PM
CSO

Jonca Bull
6/19/2006 04:04:05 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 2006

TO: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

VIA: Lisa Basham-Cruz, Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Solomon Iyasu, M.D., M.P.H., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCs Review of Patient Labeling for Opana ER (oxymorphone hydrochloride) Extended-Release Tablets, 5 mg, 10 mg, 20 mg, and 40 mg, NDA 21-610

Background and Summary

The sponsor submitted a complete response (December 22, 2005) to a Approvable Letter (October 15, 2003) for Opana ER (oxymorphone hydrochloride) Extended-Release Tablets, 5 mg, 10 mg, 20 mg, and 40 mg, NDA 21-610.

Labeling submitted included a Patient Package Insert (PPI) and the labeling was amended March 24, 2006.

Comments and Recommendations

1. See the attached PPI for our suggested revisions. We have simplified the wording where possible, made it consistent with the PI, and removed unnecessary information.
2. A PPI for Opana ER is voluntary. Unless all Opana ER product is dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that a patient will receive the PPI. The sponsor should state their mechanism for intended distribution of the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide a copy of the revised document in Word if requested by the review division. Please let us know if you have any questions.

7 Page(s) Withheld

 Trade Secret / Confidential

2 Draft Labeling

 Deliberative Process

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this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
6/14/2006 07:38:07 AM
DRUG SAFETY OFFICE REVIEWER

Solomon Iyasu
6/14/2006 08:01:36 AM
MEDICAL OFFICER

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22; Mail Stop 4447)**

DATE RECEIVED: 3/13/06	DESIRED COMPLETION DATE: 5/22/06	OSE CONSULT #: 03-0105-3
DATE OF DOCUMENT: 2/20/06 and 3/1/06	PDUFA DATE: 6/22/06	

TO: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Felicia Duffy, RN, BSN, MSED
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Opana™ (Oxymorphone Hydrochloride) Tablets 5 mg and 10 mg (Oxymorphone Hydrochloride) Injection 1mg/mL Opana ER™ (Oxymorphone Hydrochloride) Extended-release Tablets 5 mg, 10 mg, 20 mg and 40 mg NDA #s: 21-610, 21-611, 11-707	SPONSOR: Endo Pharmaceuticals, Inc.
--	--

SAFETY EVALUATOR: Felicia Duffy, RN

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary names, Opana and Opana ER provided that only one name Opana (NDA's 21-610 and 21-611) or _____ is approved. Due to the similarity in name and product characteristics between Opana and _____, we believe these products may not co-exist in the marketplace. There is a high potential for name confusion especially if both products are introduced into the marketplace in close proximity to each other. The acceptability of the proposed proprietary name Opana depends upon which application, Opana or _____, receives approval first, as these names may not co-exist due to their similarities. If the approval of Opana is delayed, the acceptability of the name will need to be re-evaluated.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary names Opana and Opana ER acceptable from a promotional perspective.

**Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 13, 2006

NDA#s: 21-610, 21-611, and 11-707

NAME OF DRUG: **Opana™**
(Oxymorphone HCl) Tablets; 5 mg and 10 mg
(Oxymorphone HCl) Injection; 1mg/mL

Opana™ ER
(Oxymorphone HCl) Extended-release Tablets; 5 mg, 10 mg, 20 mg and 40 mg

NDA HOLDER: Endo Pharmaceuticals, Inc.

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170), for a re-review of the proprietary names, "Opana" and "Opana ER", regarding potential name confusion with other proprietary or established drug names. Additionally, the sponsor is currently marketing the active ingredient oxymorphone HCl as an injection under the proprietary name, Numorphan (NDA 11-707, approved April 1959). The sponsor proposes to change the name, Numorphan, to correspond to the oral dosage formulation. Draft container labels, carton, and insert labeling were provided for review and comment.

DMETS previously reviewed the proprietary name, Opana, in a review dated August 22, 2003 (ODS consults 03-0105 and 03-0106), and found the name unacceptable based on potential confusion of Opana with Opium if the sponsor developed Opana as an oral solution. The sponsor rebutted DMETS analysis insisting that they do not plan to market Opana as an oral solution. In ODS consult 03-0105-2 and 03-0106-2, DMETS reversed the original decision and found the name Opana acceptable while considering all of the dosage forms.

PRODUCT INFORMATION:

Opana (oxymorphone HCl) is a semi-synthetic opioid whose principal therapeutic action is analgesia. Oxymorphone hydrochloride is proposed for the management of moderate to severe pain where the use of an opioid is appropriate. The immediate release dosage formulation of Opana will be available as a 5 mg and 10 mg tablet. In opioid naïve patients, the recommended starting dose of the immediate release dosage formulation is 10 mg to 20 mg every 4 to 6 hours as needed. If deemed necessary to start patients at a lower dose, patients may be started with 5 mg and may be dosed as frequently as every 2 hours. The dose should be titrated based upon the individual patient's response to their initial dose of Opana.

Opana ER (oxymorphone HCL extended-release) is indicated to the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid therapy for an extended period of time. It is not intended for use as a prn analgesia. Opana ER will be available as a 5 mg, 10 mg, 20 mg, and

40 mg tablet. In opioid naïve patients the recommended starting dose of the extended release dosage formulation is 5 mg taken orally every 12 hours. These dosage formulations of oxymorphone hydrochloride have been classified as a Class II controlled substance.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Opana/Opana ER to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving healthcare practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Opana and Opana ER. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary names, Opana and Opana ER, acceptable from a promotional perspective.
2. Since the last ODS review, the Expert Panel identified five proprietary names that were thought to have the potential for confusion with Opana and Opana ER. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage. Additionally, OPANA was identified as an acronym for the Ontario Perianesthesia Nurses Association.

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¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA).

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Opana	Oxymorphone HCl Tablets: 5 mg and 10 mg	<u>Immediate-release tablets:</u> Recommended starting dose in opioid naïve patients: 10 mg to 20 mg every 4 to 6 hours as needed.	N/A
	Injection: 	<u>Injection:</u> SC or IM: 1 mg to 1.5 mg every 4-6 hours as needed. IV: 0.5 mg initially	
Opana ER	Extended-release Tablets: 5 mg, 10 mg, 20 mg, and 40 mg	<u>Extended-release tablets:</u> Recommended starting dose in opioid naïve patients: 5 mg every 12 hours.	
			LA
Opara	Foreign drug from Pakistan	No additional information	LA/SA
Oparel	Foreign drug from Indonesia	No additional information	LA
Ipana	Toothpaste	N/A	N/A
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike) ***Name pending approval. Not FOI releasable.***			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

When this drug product was initially reviewed in ODS consults 03-0105 and 03-0106, the names submitted were Opana and Opana IR. Since prescription studies were done for Opana in our previous consult, DMETS conducted prescription studies for Opana ER only. Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Opana and Opana ER with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Opana ER (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

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HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p>Opana ER 20mg #90 i Q12</p>	<p>Opana ER Dispense #90 Take 1 tablet every 12 hours</p>
<p><u>Inpatient RX:</u></p> <p>Opana ER 20mg 1 tablet every 12 hours</p>	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed US product. See appendix A for the complete listing of the interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary names Opana and Opana ER, the primary concerns relating to potential look-alike and/or sound-alike confusion were _____, OPANA, and Ipana. DMETS would like to acknowledge that a search found two look-alike and sound-alike medications marketed in other countries: Opara, an acid pump inhibitor in Pakistan, and Oparel, a non-narcotic analgesic and antipyretic in Indonesia. Although the look-alike and sound-alike characteristics are obvious, DMETS believes the actual possibility for confusion with these product names to be minimal due to the areas of marketing. Additionally, DMETS notes that OPANA is the acronym for the Ontario Perianesthesia Nurses Association. However, we do not anticipate confusion of this organization with the proposed drug product. Furthermore, Ipana is the name of a toothpaste from the 1950's that was taken off of store shelves in the 1980's. However, it has recently reappeared in select hard-to-find stores. Ipana may look and sound similar to Opana; however, DMETS does not anticipate errors between these two products since prescriptions for Opana will contain a strength and directions for use and a prescription for Ipana is highly unlikely. If the name Ipana is written on a prescription pad, directions for use, strength, and quantity will not be indicated. Thus, the pharmacist would call the provider to clarify the order. DMETS does not have any concern with this name pair. Therefore, only _____ will be reviewed further.

Additionally, DMETS conducted prescription studies for Opana ER to simulate the prescription ordering process. In this case, there was no confirmation that Opana ER could be confused with the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Opana ER.

1. Look-alike and Sound-alike concerns for Opana and Opana ER

- a. _____ may look similar to Opana when scripted. _____ is a tradename currently pending review at the Agency. The names _____ and Opana were initially evaluated in ODS consult #04-0265. DMETS acknowledged orthographic similarities between _____ and Opana, but found _____ acceptable due to differentiating product characteristics (strength, dosing regimen, and storage conditions). However, _____ received a "Not Approvable" letter submitted January 11, 2006, for one of its indications based on the unacceptability of the safety profile for the proposed dose. Thus,

*** Name Pending approval. Not FOI releasable.

given that the dose may change, DMETS' previous acceptability of _____ will have to be re-evaluated.

_____ is indicated for the prevention of osteoporosis in postmenopausal women and for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy in postmenopausal women with low bone mass. _____ and Opana share a similar beginning (_____ vs. Opa). Additionally, the endings (_____ vs. -na) may look similar when scripted (see example below). _____ and Opana share the same route of administration (oral) and dosage form (tablets). However, _____ and Opana differ with respect to their strength (0.25 mg vs. 5 mg, 10 mg, and 1 mg/mL), frequency of administration (once daily vs. every 4-6 hours as needed), and schedules (non-controlled vs. II). Since the dose of _____ is questionable according to the Not Approvable letter, DMETS must take in to consideration that the dose and/or product strength may be similar or overlap. Post-marketing experience has demonstrated that errors do occur between drugs that share no commonalities other than a similar name especially when the prescription is ambiguously written. Thus, since both medications will be available as tablets for oral administration and may potentially overlap in dose and/or strength, DMETS is concerned that these overlapping product characteristics in addition to the orthographic similarities increase the risk of confusion and error between these products. Therefore, DMETS believes the names _____ and Opana, may not co-exist in the marketplace. There is an increased potential for name confusion especially if both products are introduced into the marketplace in close proximity to each other. DMETS has no objections to the use of the proposed proprietary name Opana provided that only one name, Opana/Opana ER (NDA 21-610 and 21-611) or _____, is approved.

Opana

- b. _____ was identified to look similar to the proposed names, Opana and Opana ER, when scripted. _____ is the proposed name (ODS Consult # 04-0268-1) for disufenton sodium, a free radical trapping agent indicated for the treatment of acute ischemic stroke. _____ is an IND pending review in the Agency. The usual dose of _____ is 151 mL/h (2265 mg) over one hour, then up to 64 mL/h (960 mg)/hr over the next 71 hours. _____ will be supplied in 20 mL glass vials and must be stored under refrigerated conditions. _____ has seven letters whereas Opana has five, however all the letters in _____ overlap with the five letters in Opana (see writing sample, page 7). The remaining two letters in _____ if not prominently scripted may be negligible in appearance. _____ and Opana ER both contain seven letters and all the letters in _____ overlap with the five letters in the root name of Opana (see below). The remaining two letters in _____ if not prominently scripted may be negligible in appearance. _____, Opana, and Opana ER vary in regards to strength (400 mg/mL vs. Opana: 5 mg, 10 mg and 1 mg/mL and Opana ER: 5 mg, 10 mg, 20 mg, and 40 mg), dosage schedule (continuous infusion for 72 hours vs. Opana: every 4 to 6 hours and Opana ER: every 12 hours), drug schedule (non-controlled vs. II), dose (2265 mg over 1 hr, then up to 960 mg/hr for 71 hours vs. Opana: 0.5 mg to 1.5 mg, and 10 mg to 20 mg and Opana ER: 5 mg to 40 mg), and storage conditions (refrigerator vs. room temperature). However, _____ and Opana ER share a common route of administration (intravenous) and dosage form (injection). Despite some orthographic similarities between _____ and Opana, the different strengths, dosages, and dosing schedules will help to differentiate the drug products. Additionally, the different storage locations will help to minimize shelf selection errors. Overall, the

*** Name Pending approval. Not FOI releasable.

differentiating product characteristics will minimize the risk of confusion between ~~_____~~
Opana, and Opana ER.

~~_____~~ AND OPANA

~~_____~~
Opana

~~_____~~
OPANA

~~_____~~ AND OPANA ER

~~_____~~
Opana ER Opana ER

2. Evaluation of the modifier "ER"

The sponsor proposes to use the modifier "ER" to identify the extended-release dosage formulation of oxymorphone hydrochloride tablets. There are currently ten drug products that utilize the modifier "ER" to distinguish the immediate-release formulation from the extended-release formulation: Depakote ER, Dynahist ER, Flagyl ER, Metadate ER, Methylin E, Ralivia ER, Razadyne ER, Trituss ER, Ultram ER, and Vospire ER. Although the specific dosing for Dynahist ER is unavailable, based on the ingredients in product, Dynahist ER is likely to be dosed twice daily. The frequency of administration for Trituss ER and Vospire ER is twice daily, whereas the frequency of administration for the remaining products is once daily. Since the precedent exists that the modifier "ER" may signify a frequency of administration of once or twice daily, DMETS believes that Opana ER is an acceptable modifier for extended-release oxymorphone hydrochloride. However, because practitioners may not recognize the dosing frequency of this product (i.e., QD vs. BID) DMETS recommends that the sponsor conduct an educational campaign in order to alert practitioners and patients on the proper use of this product.

3. Name Change of Numorphan to Opana

The sponsor is currently marketing the active ingredient, oxymorphone HCl, in an injectable dosage form under the proprietary name, Numorphan. The sponsor proposes to change the name Numorphan to Opana to correspond with the oral dosage formulation. DMETS anticipates that there may be confusion with the initial name change of the product at the time of the product launch. Correspondence with the sponsor indicates that they plan to phase out the Numorphan packaging over a period of approximately 2 months. Once the product bearing the tradename Opana reaches the ~~_____~~ distribution center, shipment of the product bearing the Numorphan tradename from the distribution center to wholesalers will cease. Any remaining inventory of Numorphan labeled product at the distribution center will be destroyed. Once the product bearing the new tradename reaches the distribution center, the sponsor will notify wholesalers that shipments of the Numorphan product has been discontinued and that the identical product (Opana) bearing the new label is available. All hospital customers will be notified of the name change via communication from their respective wholesalers. The Numorphan labeled product will be phased out as the existing supply is exhausted at the wholesaler and pharmacy levels and replaced by the product bearing the new Opana tradename. DMETS acknowledges the sponsor's efforts to minimize confusion between Numorphan and Opana by providing education and by having a streamlined plan to transition wholesalers, hospitals customers, and the distribution center from Numorphan to Opana.

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4. Confusion between Opana and Opana ER tablets

Opana and Opana ER will overlap in 5 mg and 10 mg strengths. DMETS cautions the sponsor that dispensing errors may occur due to the overlapping strengths. If a patient is ordered Opana 5 mg and receives Opana ER 5 mg, the potential exists for an overdose which can lead to an adverse reaction. Conversely, if a patient is ordered Opana ER 5 mg and receives Opana (immediate release) 5 mg, the patient will not receive adequate pain relief. Thus, it is imperative to extensively educate healthcare practitioners on the fact that two different formulations exist and to use caution when prescribing, administering and dispensing Opana and Opana ER so that the correct strength is given. Practitioners must be educated on how to switch patients from Opana (tablets) to Opana ER, and how to switch patients from Opana injection to Opana/Opana ER tablets. In addition to Opana and Opana ER sharing overlapping strengths, it is likely that these products will be stored in close proximity. This also has the potential to cause a medication error when one is in a busy clinic, pharmacy or inpatient unit where the wrong strength and formulation can be dispensed. It is important to distinguish Opana from Opana ER; thus, unique labeling and extensive education are critical in order to minimize confusion. The labeling, packaging, and product appearance can aid in the prevention of medication errors with Opana and Opana ER.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels, carton and insert labeling of Opana and Opana ER, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENT

1. DMETS notes that the labeling cites a Cmax increase of about 70% when consuming 240 mL of 40% alcohol, 31% with 240 mL of 20% alcohol, and no effect with 240 mL of 4% alcohol. The amount of oxymorphone available and the clinical symptoms after alcohol consumption will depend on the strength and dose of oxymorphone taken by the patient. Larger amounts of oxymorphone will be available with a higher strength and dose. Clinical symptoms will depend on the patient's tolerance to oxymorphone and availability of oxymorphone after dosing. Given this variance, the labeling should carry a strong warning to avoid alcohol while taking this medication. This warning should also be reiterated in the Dosage and Administration section of the Package Insert.
2. We note the color of the Opana ER 10 mg and 40 mg tablets are described in the "How Supplied" section of the package insert as light orange and yellow, respectively. The pictures of the Opana ER 10 mg and 40 mg tablets on the carton and container labels appear almost identical. Please further differentiate these colors in order to avoid confusion and errors between these two strengths.

B. CONTAINER LABEL (Blister- Immediate-release tablets [5 mg, 10 mg] and Extended-release tablets [5 mg, 10 mg, 20 mg, 40 mg])

1. Although different colored fonts are used for the different strengths on the blister labels for Opana and Opana ER, it is difficult to distinguish the proprietary names, as they appear similar on the blister. Consider using reverse lettering for Opana ER to help further differentiate the proprietary names. For example:

OPANA ER

vs.

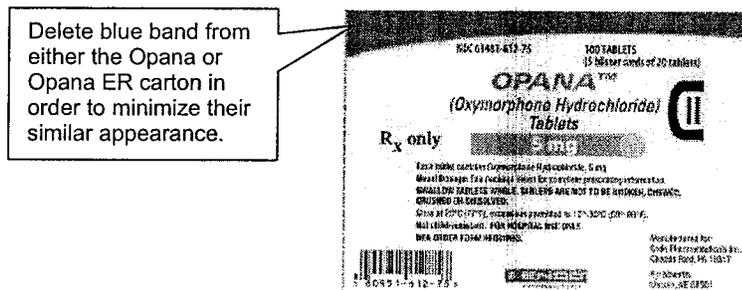
OPANA

- The trademark symbol (™) is almost as prominent as the font size used for the proprietary names, Opana and Opana ER. Decrease the size of the trademark symbol so it is not confused as part of the proprietary name.
- The font color on the blister of the Opana 5 mg (light orange) and 10 mg (light grey) tablets is too light and difficult to read. Revise the colors to appear darker in order to increase readability and contrast.
- The font color on the blisters for Opana ER 5 mg (blue) and Opana ER 20 mg (turquoise) appear very similar and is virtually indistinguishable. Revise the colors in order to clearly differentiate the two strengths in order to avoid confusion and errors.

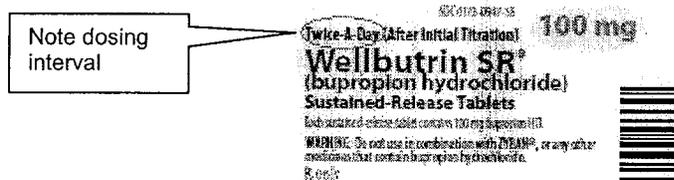


C. CARTON LABELING (Unit dose package 100 count: Immediate-release tablets [5 mg, 10 mg] and Extended-release tablets [5 mg, 10 mg, 20 mg, 40 mg])

- See comment B2.
- The blue colored band that appears at the top of the Opana and Opana ER carton labeling does not help to differentiate the drug products (Opana and Opana ER) or the product strengths. It is especially important to differentiate these drugs since they will likely sit side-by-side on pharmacy shelves, and because Opana and Opana ER overlap in strength (5 mg and 10 mg). Thus, we recommend deleting the blue band at the top of either the Opana or Opana ER label in order to minimize the similarity of the Opana and Opana ER labels.



- In order to help further differentiate the Opana and Opana ER labels, we recommend adding the dosing interval (i.e., twice-a-day) on the Opana ER label. This can be done in a similar fashion as it appears on Wellbutrin SR (see below).



4. It is difficult to distinguish the proprietary names, Opana and Opana ER, as they appear similar on the carton labeling. Consider using reverse lettering for Opana ER to help further differentiate the proprietary names. For example:

OPANA ER vs. **OPANA**

5. Decrease the prominence of the sponsor's name at the bottom of the carton as it is almost as prominent as the product strength.



F. CONTAINER LABEL (Bulk bottles: _____ 100 count, _____ : Immediate-release tablets [5 mg, 10 mg] and Extended-release tablets [5 mg, 10 mg, 20 mg, 40 mg])

1. See comments B2 and C2-C5.
2. The font color on the labels for Opana ER 5 mg (blue) and Opana ER 20 mg (turquoise) appear very similar and is difficult to distinguish. Revise the colors in order to clearly differentiate the two strengths in order to avoid confusion and errors.
3. The tablet color in the pictorial on the label for Opana ER 10 mg and Opana ER 40 mg is described as light orange and yellow, respectively. It is difficult to distinguish the colors on the container label. Ensure the colors are adequately differentiated in order to avoid confusion.

G. PACKAGE INSERT

1. Opana 5 mg and 10 mg tablets
 - a. In the Dosage and Administration section, bold the statement "Opana should be administered on an empty stomach, at least one hour prior to or two hours after eating," as this statement can be easily overlooked in all of the information presented.
 - b. In the Dosage and Administration section, bold the "Conversion from Parenteral Oxymorphone to Opana" and "Conversion from Other Oral Opioids to Opana" headings to help the reader easily locate these sections.
 - c. Repeat the Information for Patients at the end of the package insert.
2. Opana ER 5 mg, 10 mg, 20 mg and 40 mg extended-release tablets
 - a. See General Comment A1.
 - b. The Description section does not accurately define Opana ER. Revise the beginning of this section to list the active ingredient in Opana ER as oxymorphone hydrochloride extended-release rather than oxymorphone hydrochloride.
 - c. See comments G1(a) and G1(c).
 - d. The heading in the Dosage and Administration section "Conversion from Opana (IR) to Opana ER" uses the abbreviation "IR" to indicate immediate-release. DMETS does not recommend the use of the suffix "IR" to identify the immediate release dosage formulation of oxymorphone hydrochloride tablets. The use of abbreviations should be avoided when possible in order to avoid confusion or misinterpretation with other currently used modifiers or suffixes. Thus, delete the abbreviation "IR". FDA will launch a campaign in June 2006, warning health care providers and consumers not to use error-prone abbreviations. Thus, we request that the Office of New Drugs not approve or use abbreviations in their labels and labeling as they can be misinterpreted and contribute to error.

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H. PATIENT PACKAGE INSERT (Opana ER)

No comment.

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Appendix A

Prescription Study Results for Opana ER

Written Inpatient	Written Outpatient	Verbal
Opana	Opana	
Opana ER	Opana	Opana
Opana ER	Opana ER	Opana ER
Opana ER	Opana ER	Opana ER
Opana ER	Opana ER	Opana ER
Opana ER	OPANA ER	Opana ER
OPANA ER	Opana ER	Opana ER
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/s/

Felicia Duffy
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Alina Mahmud
6/9/2006 01:46:29 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/12/2006 12:10:12 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director DMETS, in her
absence

Executive CAC

Date of Meeting: June 6, 2006

Committee: Abby Jacobs Ph.D., OND IO, Acting Chair
Joseph Contrera, Ph.D., OPS, Member
Tim McGovern, Ph.D., DPAP, Member
Dan Mellon, Ph.D., DAARP, Team Leader
Mamata De, Ph.D., DAARP, Presenting Reviewer

Author of Minutes: Mamata De, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-610 Oxymorphone extended release (ER) tablets
21-611 Oxymorphone immediate release (IR) tablets
Drug Name: Oxymorphone hydrochloride (TRADENAME under review)
Sponsor: ENDO Pharmaceuticals, Inc.

Background: Oxymorphone HCl is an opioid receptor agonist. ENDO Pharmaceuticals is seeking an indication for the treatment of moderate to severe pain.

Mouse Carcinogenicity Study

Oxymorphone HCl was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day in deionized water) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day in mice was 0.35x (in males) and 0.42x (in females) times the human exposure at a dose of 260 mg (the dose for human needs to be titrated based on individual needs). No evidence of carcinogenic potential was observed in mice.

Rat Carcinogenicity Study

Oxymorphone HCL was administered to Sprague-Dawley rats (1, 5, and 10 mg/kg/day in deionized water) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day in rats was 0.34x (in males) and 1.5x (in females) times the human exposure at a dose of 260 mg. No evidence of carcinogenic potential was observed in rats.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee concurred that the study was adequate.
- The Committee concurred that the study was negative for drug-related neoplasms.

Rat:

- The Committee concurred that the study was adequate.
- The Committee concurred that the study was negative for drug-related neoplasms.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

DAARP/Division File
Mamata De/Reviewer/DAARP
Mellon/DAARP
Lisa Basham-Cruz/DAARP
ASeifried/OND IO

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Abby Jacobs

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-610

Endo Pharmaceuticals
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Bob Barto
Director, Regulatory Affairs

Dear Mr. Barto:

We acknowledge receipt on December 22, 2005, of your December 22, 2005, resubmission to your new drug application for Oxymorphone Hydrochloride Extended-Release Tablets.

We consider this a complete, class 2 response to our October 15, 2003, action letter. Therefore, the user fee goal date is June 22, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until five years after the date of approval of this NDA. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

NDA 21-610

Page 2

If you have any question, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

(See appended electronic signature page)

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Product
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lisa Basham-Cruz
1/20/2006 04:31:01 PM
For Parinda Jani



DEPARTMENT OF HEALTH & HUMAN SERVICES

MARCH 16, 2004
~~Post-Action Meeting~~
Pre-Resubmission
Public Health Service

Food and Drug Administration
Rockville, MD 20857

Endo Pharmaceuticals
100 Painters Drive
Chadds Ford, PA 19317

Attention: Robert A. Barto
Director, Regulatory Affairs

Dear Mr. Barto:

Please refer to the meeting between representatives of your firm and FDA on March 16, 2004. The purpose of the meeting was to discuss the preparation of your NDA resubmissions for Oxymorphone HCl ER Tablets, 5, 10, 20, and 40 mg (NDA 21-610), and Oxymorphone HCl IR Tablets, 5 and 10 mg (NDA 21-611).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

Sincerely,

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
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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INDUSTRY MEETING MINUTES

Meeting Date: March 16, 2004 @ 3:00pm

Location: Conference Room "C"

Sponsor: Endo Pharmaceuticals

Drug Name: Oxymorphone HCl Extended-Release Tablets (5, 10, 20, and 40 mg)
Oxymorphone HCl Immediate-Release Tablets (5 and 10 mg)

Type of Meeting: Post-Action/Pre-resubmission Meeting

Meeting Chair: Rigoberto Roca, M.D.
Division of Anesthetic, Critical Care and Addiction Drug Products

Minutes Recorder: Lisa E. Basham-Cruz, Regulatory Project Manager

Endo Pharmaceuticals	Title
Harry Ahdieh, Ph.D.	Director, Clinical Operations
Robert Barto, MBA	Director, Regulatory Affairs
Sou-Chan Chang, Ph.D.	Director, Pharmaceuticals Development
Bradley S. Galer, M.D.	Group Vice President, Scientific Affairs
Roland Gerritsen van der Hoop, M.D. Ph.D.	Group Vice President, R&D and Strategic Partnerships
Ronald J. Gerson, Ph.D., D.A.B.T.	Vice President, Development
Rosemary Kerwin, R.Ph	Manager, Scientific Communications
David A. Lee, M.D., Ph.D.	Executive Vice President, R&D/Regulatory Affairs
Tina Ma, Ph.D.	Director, Biostatistics
Carol Patterson, MS	Director, Regulatory Affairs
Mary Alice Raudenbush, MS	Vice President, Regulatory Affairs
Thomas Sciascia, M.D.	Vice President, Clinical Operations Penwest Pharmaceuticals
Dana Shuey, Ph.D., D.A.B.T.	Director, Pre-clinical Safety Assessment
FDA	Title
Bob A. Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Celia Winchell, MD	Medical Team Leader
Ravi Harapanhalli, PhD	Acting Chemistry Team Leader
Dan Mellon, PhD	Supervisory Pharmacologist
Thomas J. Permutt, PhD	Team Leader, Statistics
Dionne Price, PhD	Mathematical Statistician
Jila Boal, PhD	Chemistry Reviewer (NDA 21-610)
Dominic Chiapperino, PhD	Chemistry Reviewer (NDA 21-611)
David Lee, PhD	Biopharmaceutics Reviewer
Lisa Basham-Cruz, MS	Regulatory Project Manager

Meeting Objective: The purpose of the meeting was to discuss the preparation of the resubmissions for NDAs 21-610 and 21-611, in response to the Agency's October 15, 2003, approvable letters.

Minutes:

Following introductions, Dr. Winchell made some opening remarks. She stated that the Agency acknowledges that Endo may be apprehensive about the changes in personnel since the first review period, but assured the sponsor that the current review team has access to all prior reviews and data, and is confident that continuity between the review cycles will be maintained. Mary Alice Raudenbush expressed Endo's gratitude for the comment.

The discussion moved to discipline-specific issues and to the questions submitted by the Sponsor in their February 16, 2004, meeting packages.

Note: The Sponsor's questions are presented below in bolded text. The questions/comments are noted as referring to the extended-release (ER) or the immediate-release (IR), or both. Agency responses, prepared prior to the meeting and presented on slides, are shown in italics. Discussion is presented in normal text.

Dr. Chiapperino, Dr. Boal and Dr. Harapanhalli addressed the chemistry questions.

Oxymorphone ER & IR CMC Question 6 (re: approvable letter item 3): Will the Agency agree to accept an update to the oxymorphone monograph during the review process to include specifications for _____ impurities agreed upon between the Agency and Mallinckrodt, in the event that these have not been determined prior to submission of our full response?

FDA RESPONSE:

- *Yes. The timeliness of the update will ensure adequate time for review.*

The sponsor said that Mallinckrodt has communicated to them that an interim specification will be established for oxymorphone while efforts are underway to decrease the impurity to acceptable levels. Dr. Harapanhalli confirmed that this is correct, but that the timeline proposed to the Agency by Mallinckrodt for reaching acceptable levels must be acceptable to the Agency. The sponsor inquired about the outcome of the Division's consultation with the Genetic Toxicology Subcommittee regarding the positive gene tox findings and the implications on acceptable levels in the drug substance. Dr. Mellon responded that the Division asked for the Genetic Toxicology Subcommittee's review of the study results to confirm the Division's assessment that the finding represented a real positive result. The sponsor noted that they were under the impression that the Subcommittee was involved with setting the level of acceptable impurity. Dr. Mellon indicated that this was not asked of them. He further noted that the specification level for impurities which test positive in genetic toxicology studies is currently under discussion within the PTCC. The sponsor expressed concern that the specification issue may affect approvability of the drug product, and that they may not be adequately informed of

the status of the issue. Dr. Rappaport stated that it is Endo's responsibility to coordinate efforts with Mallinckrodt and to exchange information with them.

Dr. Chiapperino and Dr. Boal presented additional CMC comments on the IR and ER formulations, respectively.

Additional CMC comments:

- *The need for testing for the commercial batches will be assessed after review of validation batch data in the resubmission*

Oxymorphone IR CMC Comments (contd.)

- *Regarding discussion of CMC comment 5(e) pertaining to dissolution (p.32-33), the Division cannot comment as yet on your intention of leaving the acceptance criterion unchanged without evaluation of your new data from validation batches. We reiterate our concern that meaningful data would not be captured at 30 minutes for very rapid tablet dissolution. Based on the time profile curves for dissolution, appropriate time-point and Q will be recommended in the next review cycle.*

Oxymorphone ER CMC Comments (contd.)

Regarding discussion of CMC comment 5(2) ii pertaining to drug product dissolution (p.24-25).

- *Provide drug release data on core tablets with samples collected for the first 3 commercial batches in addition to the validation batches.*
- *Provisions such as test sunseting and product quality intermittent testing (PQIT) would be considered based on the results of the recommended testing.*

Oxymorphone ER & IR Preclinical Question 5 (re: approvable letter item 2): Will demonstration of an associate with hyperthermia, if successful, satisfy the Agency's desire for additional information on the mechanism of oxymorphone-induced micronuclei?

FDA RESPONSE:

- *In part.*
 - *Provide scientific rationale for your explanation in the context of the existing literature describing the mechanism of morphine-induced micronuclei (i.e., incorporate the existing literature into the hypothesis).*

- *Describe how opioid-induced temperature regulation in the rat and mouse are similar in the context of the magnitude, timing and direction of the temperature change.*
- *If the hypothesis fits the existing data, the studies should satisfy the Agency's request.*

The sponsor indicated that their data conclusively show that effect of oxymorphone on micronuclei formation was completely blocked by sodium salicylate and therefore they feel that the data indicate the effect is due to temperature changes. Dr. Mellon indicated that that data would be supportive of their hypothesis. However, he noted that opioid effects on temperature regulation are complex. Specifically, the effect is species-dependent, dose-dependent and time-dependent. As such, Dr. Mellon requested that the sponsor carefully examine their hypothesis and make sure that it survives scrutiny. The sponsor should thoroughly characterize the response. For example, the effect of oxymorphone likely requires reaching a certain magnitude of temperature change for a specific duration of time in order to produce increased micronuclei. Therefore, if the temperature must be increased by 5 degrees to produce micronuclei, but the dose of oxymorphone that produces micronuclei only increases temperature by 3 degrees, their hypothesis would be questioned. The sponsor indicated that they would provide a definitive response.

Dr. Mellon elaborated on his request that the sponsor address the existing hypothesis that morphine-induced micronuclei were opioid-receptor dependent largely the result of activation of the HPA axis. He indicated that this request was the result of the sponsor's September 30, 2003 submission that discussed the genetic toxicology findings. In that submission, the sponsor indicated that they believed the increased micronuclei were the result of a class effect and thus could be attributed to the same mechanism as proposed for morphine. Dr. Mellon requested that the sponsor address why they feel that their initial assessment is no longer true and discuss their results in light of the published literature as part of the NDA submission.

Dr. Price addressed clinical question 1 for the extended-release formulation.

Oxymorphone ER Clinical Question 1 (re: approvable letter item 1a): Does the Agency agree that results of the alternate analysis confirm the original protocol-defined analyses of EN3202-015 and EN3202-025, support an overall treatment effect for oxymorphone ER over placebo, and together with study EN3202-016 adequately demonstrate compelling evidence of efficacy of the product in the population that this product is intended to treat?

FDA RESPONSE:

- *Alternative statistical approaches were submitted to offset the concern regarding the potential of the missing data strategy to artificially inflate the effectiveness of the drug without accounting for possible intolerability of the treatments.*

Table: 4 Alternative Approaches

<i>Method 1</i>	<i>Direct substitution</i>	<i>Does not address concern</i>
<i>Method 2</i>	<i>Mean of all Data</i>	<i>Does not address concern</i>
<i>Method 3</i>	<i>Adjusted LOCF</i>	<i>Reasonable alternative</i>
<i>Method 4</i>	<i>Mixed Model Repeated Measures</i>	<i>Does not address concern</i>

- The alternate analysis allows study EN3202-025 to be interpreted as supportive of an overall treatment effect for oxymorphone ER, but a finding of efficacy cannot be supported for any specific dose lower than 50 mg. Therefore, it does not provide the needed confirmation of the efficacy findings of Study EN3202-016.*

Dr. Price summarized the four alternative statistical approaches submitted by the sponsor. She stated that method 1 (an averaging method) might not inflate the effectiveness of the drug as much as the LOCF methodology; however, the method still appeared to impute good scores to some patients who dropped out. Dr. Price further stated that method 2 utilized the same strategy for handling missing data due to adverse events as method 1, but with the averaging scheme applied to all participants regardless of completion or discontinuation. Method 4 employed a mixed model repeated measures strategy. This strategy is reasonable if the missing data occurs randomly so that missingness is noninformative. However, the missing data from studies 15 and 25 was potentially informative; therefore, method 4 did not address the Division's concern.

Dr. Price stated that method 3, the adjusted LOCF methodology, was the most reasonable strategy proposed by the sponsor to address the Division's concern. The analysis used a LOCF imputation scheme; however, the derived change from baseline was subsequently adjusted by a factor that reduced the magnitude of the change depending on the time of withdrawal.

The sponsor explained that method 1, like method 3, essentially assumed no change in pain score subsequent to withdrawal. Dr. Price suggested that this explanation of method 1 differed from the Division's understanding of the methodology based on the submitted materials. However, even with method 1, study 15 would still not demonstrate treatment effectiveness based on the reanalysis. The sponsor then focused attention on the rank transformed analysis (referred to as non-parametric by the sponsor) for study 15. Dr. Price responded that the ANCOVA was robust with respect to moderate departures from the basic assumptions; therefore, the assumption of normality could be relaxed. Consequently, the transformation was not necessary.

Attention then focused on study 25. The sponsor believed that study 25 provided evidence of an effect for the 40-mg and 50-mg doses as opposed to only the 50 mg arm as stated by the Division. The belief was formulated based on the original NDA submission as well as results obtained using methods 1 and 3. The sponsor stressed that the primary analysis of study 25 employed a trend test which assessed efficacy over a range of doses. The Division agreed to revisit study 25 after further internal evaluation and consideration of method 1. Dr. Price expressed concern that most participants discontinued in the initial weeks of the studies (during titration); therefore, the averaging of method 1 did not provide an indication of the pain score at the randomized dose.

Additional discussion related to the validity of method 4. Dr. Price restated the Division's position on the inappropriateness of method 4 due to the concern for informative missing data. Discussion concluded with an agreement by the Division to revisit method 1 as a possible reasonable alternative approach to handle missing data.

The following comments are in response to the sponsor's meeting minutes submitted on April 9, 2004.

A few points warrant additional clarification by the Division. The submitted minutes on page 4 state, "B. Galer stated that the four methods adequately take into account drop-outs and punish patients appropriately, consistent with the agreement of the teleconference (October 31, 2003)." As a result of the teleconference, the Division agreed to consider additional proposed methods. Alternative methods would be evaluated by the Division based on the appropriateness of the methodologies to address the Division's concern. Moreover, a collective evaluation of all of the evidence would be conducted by the Division.

The sponsor's description of the dialogue frequently referenced the "penalty" of the methods. Dr. Price refrained from such terminology during the meeting. The concern was not that patients were penalized but rather that the score assigned to patients best described the effect of the drug on patients. Moreover the minutes on page 5 state, "Both B. Galer and D. Price agreed that method 3 was valid." Dr. Price stated the method was a "reasonable" strategy to address the Division's concern.

Additionally the minutes on page 4 state, "B. Rappaport states it was his understanding that these methods appear to be somewhere in the middle of these two extremes and asked if Endo could quantify the amount of punishment applied to each method." During the course of the meeting, Dr. Rappaport asked for clarification. He responded that based on the sponsor's dialogue concerning methods 1 and 2, he understood the sponsor's assertion that the methods were somewhere in the "middle" between the LOCF and BOCF methodologies. The minutes on page 5 state, "D. Price said that she will reconsider Method 1 but that the p-values are still too borderline for 40 mg." Dr. Price stated that p-value resulting from method 1 (for study 25) was borderline significant for the 40-mg dose.

Oxymorphone ER Clinical Question 2 (re: approvable letter item 1a): Does the Agency agree that no additional studies are necessary?

FDA RESPONSE:

- *Additional efficacy data will still be necessary.*

Dr. Rappaport noted that for reformulated opiates, the Agency has been requiring efficacy data for the lowest effective dose and higher. Lower doses without efficacy data may be listed in the label for titration, but cannot be labeled as effective. The product is a New Drug and the information needed to write labeling is not available. Additional data is needed to define the

lowest effective dose. Dr. Rappaport agreed to revisit the statistical data for the Extended-Release formulation by reevaluating the use of method 1 in conjunction with method 3.

Oxymorphone IR Clinical Question (re: approvable letter item 1): The sponsor is mindful of the fact that the Agency will not review this study until it has been formally received as part of the Complete Response to the Approvable Letter. Does the Agency agree that the new clinical trial EN3202-008 on its face will be responsive to the Agency's request for an additional study that includes data on multiple dosing?

FDA RESPONSE:

- *Reviewers identified uncertainty regarding proper dosing interval, and requested an additional multiple-dose trial to address this. Dosing interval of 8 hours was found inappropriate from efficacy standpoint but reviewers raised concern about dosing q 4-6 hours from safety standpoint.*
- *In study EN3202-008, outpatients self-titrated using 5 mg q 1 hour P.R.N. This does not appear to provide any further information about the proper dosing interval for doses >5 mg.*

Oxymorphone IR Clinical Question (re: approvable letter item 1): The sponsor asserts that if clinical trial EN3202-008 is found by the Agency to demonstrate the efficacy of 5 mg oxymorphone IR, the results of this trial along with data from previous studies that will be provided in the updated integrated Summary of Effectiveness will provide adequate evidence for the efficacy of the product in the intended patient population over the 5-20 mg dose range. Does the Agency concur?

FDA RESPONSE:

- *Study EN3202-008 used self-titrated dosing*
 - *Although the study provided the subjects with a 5 mg dosage form, subjects who remedicated repeatedly within the 8 hour study cannot be described as treated with a 5 mg dose.*
 - *Data from the 1 hour time point might conceivably provide data supporting efficacy of a single 5 mg dose for ONE hour, but would need replication and do not support labeling of 5-20 mg q 4-6 hours.*
 - *The one-hour data may be helpful in providing support for a dose of 10 mg (not otherwise replicated in the efficacy database), but the dosing interval remains to be determined.*
 - *The 8-hour data represents subjects using a wide range of doses and intervals and is unlikely to support a claim for a particular dose or interval.*

Clinical Question (re: approvable letter item 1): Does the Agency agree that the new analysis on dosing interval, along with the pharmacokinetic data, allows the sponsor to label the dosing recommendation appropriately and therefore no additional studies are required?

FDA RESPONSE:

- *Descriptive information from Study 004 does not support either the efficacy or the safety of the dosing interval proposed,*
 - *design issues precluded the use of data from the multiple-dosing phase to support efficacy conclusions*
 - *the pattern of occurrence of adverse events in this study suggest that the actual dosing interval may be problematic*
 - *PK data also suggest that dosing at 4 hour intervals may lead to accumulation.*
- *Additional safety data on the proposed q 4-6 hour interval are needed.*

Dr. Winchell noted that the descriptive information about the actual dosing intervals employed in the study encompassed a very small number of patients to begin with: Only 104 subjects were included in descriptive table, and, of these, only 89 took more than one dose and therefore had at least one “interdose interval”; and only 76 had more than one dosing interval to contribute to the analysis. Eight of the 89 subjects who took more than one dose discontinued due to adverse events, many of which appear drug related, giving an unacceptably high rate of discontinuation of approximately 10 %. The sponsor surmised that many of these patients may have been in the 30-mg arm and agreed that the 30-mg dose group had an unacceptable number of AEs. Dr. Winchell noted that removal of the 30-mg dose group, however, resulted in even fewer patients to evaluate the interdose interval, rendering observations about the actual dosing interval employed by this subgroup unsuitable to support prescriptive conclusions regarding the appropriate interval.

Oxymorphone ER & IR Clinical Question 3 (re: approvable letter item 1b): Does the Agency agree that concerns with liver function, WBC, and QTc interval raised during the review of the NDA will have been adequately addressed with the data provided in this package?

FDA RESPONSE:

- *The information offered on hepatic enzyme elevations and neutrophil abnormalities appears responsive to the Division’s concerns.*
- *The information offered on ECG abnormalities does not assuage the Division’s concerns about the abnormalities seen in the limited available data. If no additional information is*

available from existing datasets, further evaluation of the ECG effects of oxymorphone is warranted.

Dr. Winchell noted that QT intervals were available only for the 58 subjects who participated in the three Phase 1 studies where EKGs were recorded. Only assessments of “normal” and “abnormal” were available for the 568 subjects who participated in the three Phase 2/3 studies in which EKGs were recorded. She continued that, among the 58 subjects with available QT intervals, the review identified 6 subjects with at least one increase (from pre-dose to post-dose) of at least 30 msec. All of these ECGs were rated as ‘Normal’ by the investigator. Among these were two with prolongations >100 msec with post-treatment values of 476 msec and 491 msec. Dr. Winchell acknowledged Endo’s belief that “no cardiac safety concerns were observed in the oxymorphone program.” This is based on the absence of any subject with a QTc interval >500 msec on treatment, the absence of any report of an adverse event of torsade de pointes, syncope, sudden death, ventricular fibrillation, or ventricular tachycardia, and the assertion that a clinical literature review does not support an association between the opioid class and QTc prolongation or torsade de pointes. Dr. Winchell noted, however, that some opioids are known to cause QT prolongation, and that prolongations of <500 msec are significant in a population of this size (note: only 58 subjects have documented QT intervals). She continued that there were in fact two subjects with reports of syncope (EN3202-012-012-008, placebo, and EN3202-025-007-010, oxymorphone 20) as well as three subjects (EN3202-016-006-004, EN3202-025-006-006, EN3203-004-003-001, all treated with oxymorphone) for whom a verbatim term of “faint feeling” or “feeling faint” was recorded. (These terms were coded to “dizziness” under the MEDRA coding system.) One subject treated with oxymorphone reported loss of consciousness (EN3202-020-013-002). In addition, palpitations and tachycardia were among terms reported in association with oxymorphone exposure. The ISS database lists 14 reports of “palpitations,” 13 of which were associated with oxymorphone ER and one with oxymorphone IR. No other treatment arm (e.g. morphine, oxycodone, or placebo) is associated with reports of palpitations.

Dr. Winchell stated that these findings cannot be ignored. She suggested that the sponsor concentrate on explaining the six cases detailed above. The sponsor responded that it was unlikely that those subjects had blood levels of drug when the AEs occurred and that they may have pharmacokinetics data to support this. Dr. Rappaport noted that QT effects can occur some time after Cmax. The sponsor said that they will attempt to provide an explanation for the ECG data. If this cannot be accomplished, they will provide data from a ECG study, of the type described in recent agency documents concerning the evaluation of drug effects on cardiac conduction.

Oxymorphone ER & IR Clinical Question 4: Does the Agency agree that the proposed format and content of the safety update is acceptable?

FDA RESPONSE:

- *The format appears acceptable.*

ACTION ITEMS:

- 1) The Division will revisit the statistical data for the Extended-Release formulation by reevaluating the use of method 1 in conjunction with method 3. The evidence will subsequently be evaluated collectively to determine whether another study will be required. POST MEETING NOTE: A teleconference is scheduled for May 5, 2004, to inform the sponsor of the Division's conclusions.
- 2) Another study will be required for the immediate-release formulation in order to support the 4-6 hour dosing interval. Endo will submit this protocol as a Request for Special Protocol Assessment and include details regarding the statistical analysis plan.
- 3) Endo will look for pharmacokinetic data to explain the ECG data, and will perform a study, if necessary, to evaluate cardiac effects of the drug. Dr. Lee requested that Endo provide detail about the specific method used to correct QT interval.

- Lisa E. Basham-Cruz
Regulatory Project Manager

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this page is the manifestation of the electronic signature.**

/s/

Lisa Basham-Cruz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Post Action Mtg
CMC 12/29/03

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-610
NDA 21-611

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

Attention: Robert Barto
Director, Regulatory Affairs

Dear Mr. Barto:

Please refer to the teleconference between representatives of your firm and FDA on December 1, 2003. The purpose of the teleconference was to provide clarification on the CMC comments in the October 15, 2003 approvable letters.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

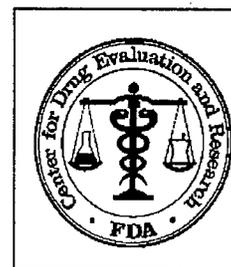
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Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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Industry Meeting Minutes



Date/Time: December 1, 2003

Location: Teleconference

Application: NDA 21-610; Oxymorphone Extended-Release Tablets
NDA 21-611; Oxymorphone Immediate-Release Tablets

Sponsor: Endo Pharmaceuticals

Type of Meeting: Type A Post Action

Meeting Chair: Ravi Harapanhalli, Ph.D..
Acting Team Leader, Chemistry, Manufacturing, and Controls (CMC)

Minutes Recorder: Parinda Jani, Chief, Project Management Staff

Sponsor Attendees	Title
Mary Alice Raudenbush	Vice President, Regulatory Affairs
Sou Chan Chang	Director, Pharmaceutical Development
Michele Howard Sparks	Senior Technical Operations Specialist
Carol Patterson	Director, Regulatory Affairs, CMC
FDA Attendees	Title
Sharon Hertz, M.D.	Clinical Team Leader
Ravi Harapanhalli, Ph.D.	Acting Chemistry Team Leader
Dan Mellon, Ph.D.	Pharmacology/Toxicology Team Leader
Jila Boal, Ph.D.	Chemistry Reviewer
Dominic Chiapperino, Ph.D.	Chemistry Reviewer
Parinda Jani	Chief, Project Management Staff

Minutes:

The discussion centered on the questions submitted with the November 5, 2003, meeting request. The Action Letter Items refer to specific items noted in the October 15, 2003, action letters, and are presented below (bolded), followed by the Applicant's response and questions (italicized). Discussion is presented in normal text.

Action Letter Item # 3 (for both products)

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.

Sponsor's Response:

The sponsor requested clarification for the requirements for 2-week repeat dose toxicity studies for the impurities indicated. The letter implies that these studies may be required even if specification for each drug product is lowered to NMT [redacted].

Discussion: Dr. Mellon clarified the comment. The Division would like the sponsor to either reduce the impurity level to NMT [redacted] or qualify the impurity. If the specification is set to NMT [redacted], then a study would not be required.

Action letter item 5b(1)iii, 5b(2)i for NDA 21-611

- b. The following [redacted] tests should be performed on a routine basis in every commercial production of the extended-release tablets:

[redacted]

8

Sponsor's response:

The sponsor needs clarification as the comment requests that the sponsor perform [redacted] tablet sampling and testing. As per the PQRI [redacted] Working Group, recommendation for [redacted], if all acceptance criteria are met for [redacted] core tablets during the validation of commercial manufacturing process, the [redacted] dosage units (core tablets) for routine production batches should be sufficient [redacted]. Is this understanding correct?

Action letter item 5c(2) for NDA 21-611

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

[redacted]

Sponsor's response:

Both products will be manufactured at the same manufacturing site. However, the Agency has requested [redacted] for the extended release product, but [redacted] and sampling plan for the immediate release product. As per the PQRI [redacted] Working Group, recommendation for [redacted], if all acceptance criteria are met for [redacted] core tablets during the validation of commercial manufacturing process, then [redacted] dosage units (core tablets) for routine production batches should be sufficient in

_____ . It is not clear whether the Agency is requesting
_____ for the IR tablet as well.

Discussion: Dr. Harapanhalli had the following comments for both products.

The requirements _____
which are _____ controls, should apply to both products. _____ analysis is required under CGMP.
Oxymorphone has a narrow therapeutic range and is formulated at low percent strength in the
formulation (_____ active). Also, the to-be-marketed products will be available in low
strengths of 5, 10, 20 and 40-mg. The proposed PQRI guidance document on _____ analysis may not be
comprehensive in addressing the _____ issues of drugs that are highly potent, of narrow therapeutic
range formulated at low percent composition, tablets made by _____
_____, and IR vs MR products.

The sponsor responded that they have manufacture 3 validation batches of each drug product. Based on
the data, they would like to drop one of the tests for the commercial batches.

Dr. Harapanhalli responded that we would review the data collectively. If the data are satisfactory, and
the sponsor has demonstrated that the manufacturing is under control, a CMC supplement could be
submitted post approval for dropping one of the test, _____
on the finished product. Until then _____ should be performed on both IR and ER
products on a routine bases, including for commercial batches. He also reiterated that product quality
intermittent testing (PQIT) and test sunsetting are other viable options down the line.

The telecon adjourned at 2:45 PM

Action Items:

1. Sponsor to provide data (_____) on the registration/validation batches
in response to these deficiencies in the complete response.
2. Sponsor to also provide data on the _____
excipients and the _____ as requested in the action letter.

Minutes prepared by:

Parinda Jani

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

/s/

Parinda Jani
12/29/03 11:04:13 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Post Action Mtg
11/26/03
Public Health Service
CLINICAL

Food and Drug Administration
Rockville, MD 20857

NDA 21-610
NDA 21-611

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

Attention: Robert Barto
Director, Regulatory Affairs

Dear Mr. Barto:

Please refer to the meeting between representatives of your firm and FDA on October 31, 2003. The purpose of the meeting was to provide clarification on the clinical comments in the October 15, 2003 approvable letters.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

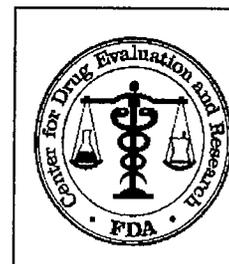
Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz
Regulatory Project Manager
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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MEETING MINUTES

Meeting Date: October 31, 2003

Location: Teleconference

Application: NDA 21-610; Oxymorphone Extended-Release Tablets
NDA 21-611; Oxymorphone Immediate-Release Tablets

Sponsor: Endo Pharmaceuticals

Type of Meeting: Type A Post Action (clinical)

Meeting Chair: Sharon Hertz, M.D.
Division of Anesthetics, Critical Care, and Addiction Drug

ATTENDEES:

FDA:

Sharon Hertz, MD	Medical Team Leader, Analgesics and Neuropathy
Gerald DalPan, MD	Medical Reviewer
Dionne Price, PhD	Mathematical Statistician
Tom Permutt, PhD	Team Leader, Mathematical Statistician
Lisa Basham-Cruz, MS	Regulatory Project Manager

Endo Pharmaceuticals:

Harry Ahdieh, PhD	Director, Clinical Operations
Robert Barto	Director, Regulatory Affairs
Bradley S. Galer, MD	Vice President, Scientific Affairs
Roland Gerritsen van der Hoop, MD, PhD	Group VP R&D, Strategic Partnerships
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Minutes:

The discussion centered on the questions submitted with the October 20, 2003, meeting request. The Action Letter Items refer to specific items noted in the October 15, 2003, action letters, and are presented below (bolded), followed by the Applicant's response and questions (italicized). Discussion is presented in normal text. The extended-release formulation was discussed first.

Action Letter Item 1 (NDA 21-610; Oxymorphone Extended-Release Tablets)

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.**

Sponsor's Response:

- 1) The Agency indicates that Studies EN3202-015 and EN3202-025 do not provide compelling evidence of efficacy. Could you please provide more details on how the Agency came to this conclusion? More specifically,
 - *What analyses did you perform to determine efficacy?*
 - *What population did you include in your analyses?*
 - *What criteria did you use to define 'compelling'?*
 - *Were there any non-statistical issues related to efficacy that caused concern? If so, could you please specify what they were?**
- 2) What specific safety concerns were raised in Study EN3202-012 regarding the use of oxymorphone ER in post-operative patients? In what way did these safety concerns affect the use of this study to support efficacy?*
- 3) What specific concerns does the Agency have regarding oxymorphone's effects on liver function tests, WBC count, and QTc interval? Can you be more specific as to what particular data contributed to these concerns?*

Discussion:

- 1) Dr. Hertz addressed the efficacy issues by saying that overall, the Division believes there is some evidence of efficacy for both the ER and IR formulations, but the data did not adequately support efficacy and safety of the drugs. Study EN3202-016 showed some evidence of efficacy. Study EN3202-012 showed some efficacy, but the patient population in this study was not the population that this drug is intended to serve, and there were safety issues with this study. Studies EN3202-015 and EN3202-025 had failed to adequately demonstrate efficacy.

Dr. Price explained that the main concern with the efficacy findings of EN3202-015 and EN3202-25 was the use of the Last Observation Carried Forward (LOCF) method for handling missing data. Due to the disproportionately high number of patients discontinuing

in the treatment arms (as compared to placebo), a LOCF strategy may have artificially inflated the effectiveness of the treatment without accounting for the intolerability of the treatment. Upon reanalyzing these studies using a different imputation scheme, i.e. Baseline Observation Carried Forward (BOCF), there was no treatment effect, suggesting that the results were sensitive to the method of imputation. Dr. Price additionally replied to bullet two above. She stated that the analysis population included all randomized patients receiving study medication (with the exclusion of the site experiencing a drug diversion).

Dr. Hertz explained that the term “compelling” is meant to mean “substantial enough,” and in this case, the findings from study EN3202-016 have not been substantially replicated to support a claim of efficacy. The applicant responded that the BOCF method seems extreme in that it assigns a “0” improvement to dropouts. They suggested that perhaps a sensitivity analysis that penalizes dropouts, but not to the extent of assigning zero, might be more reasonable. The sponsor asked if the Division would be willing to consider additional analyses. Dr. Price responded that there is no single statistical method recommended for analyzing data in the presence of missing information and that the Division would be willing to consider additional analysis methods. Dr. Permutt also acknowledged that the BOCF method is only one possible imputation strategy; however, the goal of employing any alternative imputation scheme is to achieve consistent results. When using the BOCF strategy, the treatment effect did not just wane, but disappeared altogether. He continued that the Division will consider any alternative method the sponsor wishes to propose, but noted that the Division will collectively evaluate all of the evidence.

Dr. Hertz responded to the fourth bullet above by saying that the data did not meet the criteria of providing substantial efficacy, i.e., replicated efficacy demonstrated in an appropriate population.

- 2) Dr. DalPan addressed Question 2 by noting the high number of patients requiring naloxone in the post operative period, i.e., 4/66 in the ER studies and 12/334 in the IR studies as a result of excessive CNS depression and/or respiratory depression. These occurrences indicate that the use of ER in this setting may not be appropriate and that appropriate dosing of IR in this setting is not well understood.
- 3) Dr. DalPan explained that concern about LFT, WBC, and QTc arose late in the review. Seven subjects demonstrated clinically significant neutropenia (some with follow-up and some without). The Division will send a list of specific subjects and lab values that were of concern.

There were a number of patients with normal LFTs at baseline, but clinically significant LFT abnormalities (both AST and ALT) at follow-up. Regarding QTc intervals, initially the ISS did not contain an analysis of ECG data. Dr. DalPan requested this information and received mean and other descriptive values from the sponsor. When individual patient values were evaluated, there was evidence of clinically significant elevations in QTc interval, some by as much as 100 msec.

Dr. DalPan stated that he would provide a table containing details of his findings.

The discussion turned to the Immediate-Release formulation.

Action Letter Item 1 (NDA 21-611; Oxymorphone Immediate-Release Tablets)

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.**

Sponsor's Response:

- 1) Could you please elaborate on the need for an additional study? It is our understanding that we were to submit two adequate and well-controlled trials in support of oxymorphone IR. In our opinion, Studies EN3203-004 (multiple-dose) and EN3203-005 (single-dose) demonstrated the safe and effective use of oxymorphone IR in the post-operative setting and provided data showing the safe and effective dosing interval.*

Discussion:

Study -004 demonstrated single-dose efficacy, but in the multiple-dose phase, there was no difference between high dose, low dose, and the comparator. The two efficacy trials demonstrated single-dose efficacy, but a number of patients required naloxone, which implies that the manner in which they were dosed may not be appropriate. The efficacy of the 10-mg dose has not been replicated, and the 30-mg dose showed no advantage over the 20-mg dose. Furthermore, in a monitored setting, there was a relatively high level of opiate antagonist use. Use in the outpatient setting would be even more dangerous. The dosing interval of 6-8 hours may not be appropriate. Studies -004 and -005 had a large number of dropouts (>50%) within 4-5 hours. Study -004 describes a 7-9 hour dosing interval, but rescue medication was allowed, so the observed dosing interval does not reflect the effects of the oxymorphone alone. The pharmacokinetic data could support a shorter dosing interval, but there is no safety data for a 4-6 hour dosing interval. Therefore, there are still many questions about appropriate dosing of this drug.

Action Items:

The Division will provide a table of Dr. DalPan's safety findings to the sponsor (attached; emailed November 3, 2003)

The sponsor will explore reanalysis methods and submit to the Division for consideration.

- Lisa E. Basham-Cruz
Regulatory Project Manager

NDA 21-610 Oxymorphone HCl ER Tablets
 NDA 21-611 Oxymorphone HCl IR Tablets

Information for Sponsor on LFT, WBC, and QTc Values

The table below summarizes neutrophil values of concern in Phase 1 studies:

Table. Cases of Treatment-Emergent Neutropenia					
Subject ID	Treatment	Baseline		On Treatment	
		WBC*	Absolute Neutrophil Count*	WBC*	Absolute Neutrophil Count*
EN3202-005-001-002	Oxymorphone ER	4.9		4.4	
EN3202-009-001-001^	Oxymorphone ER	6.4		5.4	
EN3202-009-001-010	Oxymorphone ER	6.0		4.0	
EN3202-009-001-019^	Oxymorphone IR	5.5		3.4	
EN3202-009-001-022	Oxymorphone ER	7.7		6.7	
EN3202-009-001-026	Oxymorphone ER	7.3		2.9	
EN3202-009-001-028#	Oxymorphone ER	7.1		1.6	

* X10³/mm³
 ^ Follow-up neutrophil value normal
 #Follow-up WBC value normal, but no differential count reported

Source: Appendices 10.10 and 10.11 in the ISS

The following tables summarizes AST and ALT data for subjects with normal values of both enzymes at baseline who subsequently developed clinically significant abnormalities of both values enzymes-baseline,

Table. Subjects with Treatment Emergent, Clinically Significant Abnormal Elevations of Both AST and ALT.							
Subject ID	Protocol	Treatment	Study Day	Lab Test	On Study	Baseline	Comments
EN3202-012-019-006	EN3202-012	Oxymorphone ER	2	ALT	177	16	No follow-up values available. Adverse events describing increased AST and increased ALT judged these events to be moderate in severity, possibly related to study drug, and outcome unknown. Investigator notes that this may be possibly due to study drug.
				AST	173	20	
EN-3202-012-022-010	EN3202-012	Oxymorphone ER	2	ALT	264	12	No follow-up labs available. Investigator notes that this may be due to the surgical procedure (left knee arthroplasty), but provides no further rationale for this opinion.
				AST	438	14	
EN3203-004-021-006	EN3203-004	Oxymorphone IR	1	ALT	229	16	No follow-up labs available
				AST	236	20	
EN3203-004-021-011	EN3203-004	Oxymorphone IR	2	ALT	142	26	No follow-up labs available
				AST	156	31	
EN3202-016-012-003	EN3202-021	Oxymorphone ER	97	ALT	220	19	Subject discontinued due to adverse event "Increased liver enzymes", judged by investigator to be moderate in intensity and unlikely related to study drug. GGT was also elevated (180 U/L normal range: 10-61). No further detail are available
				AST	236	14	

Source: Appendix 10.11 in the ISS

The following table summarizes clinically significant QTc abnormalities in three Phase 1 studies (EN3202-001, EN3202-002, and EN3202-003), defined for the purposes of this exploratory analysis of the ISS data as QTc interval ≥ 430 msec (males) or 450 msec (females) or a change from pre-dose of ≥ 30 msec. In this analysis, the 'Change' values refers to a change from pre-dose to post-dose. Note that this table includes both pre-dose as well as post-dose abnormalities in QTc values.

Table. ECG Measures for Phase I Subjects With Clinically Significant QTc Interval Abnormalities

Subject ID	A/G/R#	Treatment [^]	Heart Rate			PR Interval (msec)			QRS Interval (msec)			QT Interval (msec)			QTc Interval (msec)		
			Pre-Dose	Post-Dose	Change	Pre-Dose	Post-Dose	Change	Pre-Dose	Post-Dose	Change	Pre-Dose	Post-Dose	Change	Pre-Dose	Post-Dose	Change
EN3202-001-001-010	34/M/C	OM ER	87	65	-22	162	144	-18	96	95	-1	360	374	14	433*	389	-44
EN3202-001-001-011	23/M/C	OM ER	54	45	-9	125	139	14	98	92	-6	475	456	-19	450*	394	-56
EN3202-001-001-011	23/M/C	OM ORAL SOL	52	41	-11	132	135	3	98	98	0	474	430	-44	441*	355	-86
EN3202-002-001-001	22/M/C	OM ER	56	40	-16	144	149	5	103	108	5	386	584	198	372	476*	104*
EN3202-002-001-001	22/M/C	OM ER	56	41	-15	190	151	-39	111	96	-15	455	420	-35	439*	347	-92
EN3202-002-001-006	22/M/C	OM ER	66	55	-11	160	153	-7	95	96	1	342	513	171	358	491*	133*
EN3202-002-001-009	25/M/C	OM ER	82	77	-5	174	179	5	104	102	-2	405	370	-35	473*	419	-54
EN3202-002-001-009	25/M/C	OM ER	80	82	2	168	174	6	97	97	0	350	383	33	404	447*	43*
EN3202-003-001-002	19/M/C	OM ER	55	54	-1	153	175	22	81	83	2	400	435	35	382	412	30*
EN3202-003-001-005	24/M/C	OM ER	53	50	-3	145	145	0	102	97	-5	448	475	27	421	433*	12
EN3202-003-001-005	24/M/C	OM ORAL SOL	54	53	-1	145	125	-20	100	102	2	496	471	-25	470*	442*	-28
EN3202-003-001-006	36/M/C	OM ORAL SOL	71	75	4	127	144	17	83	82	-1	466	361	-105	506*	403	-103
EN3202-003-001-012	21/M/A	OM ORAL SOL	58	67	9	170	168	-2	90	92	2	334	372	38	328	393	65*
EN3202-003-001-020	33/M/C	OM ER	108	91	-17	144	154	10	102	104	2	323	345	22	433*	424	-9
EN3202-003-001-027	30/M/B	OM ORAL SOL	59	64	5	202	193	-9	94	90	-4	378	413	35	374	426	52*

#A/G/R=Age/Gender/Race

[^]OM ER=Oxymorphone ER tables, OM ORAL SOL=Oxymorphone Oral Solution

*Clinically significant QTc abnormality is a QTc interval ≥ 430 msec (males) or 450 msec (females) or a change from pre-dose of ≥ 30 msec.

Source: Sponsor data in datafile iss_ecgs.xpt, as analyzed by FDA medical reviewer. See also Appendix 8.12 in EN3202-001 study report and Appendix 8.12 in EN3203-002 study report.

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Lisa Basham-Cruz
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