

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 201-655  
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Product: Oxymorphone HCl (b) (4) Extended-Release Tablet  
Indication: Relief of moderate to severe pain in patients requiring continuous opioid therapy for an extended period of time  
Applicant: Endo Pharmaceuticals  
Review Division: Division of Anesthesia and Analgesia Products  
Reviewer: Elizabeth A. Bolan, Ph.D.  
Supervisor/Team Leader: R. Daniel Mellon, Ph.D.  
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# 1 Executive Summary

## 1.1 Recommendations

### 1.1.1 Approvability

This NDA can be approved from a pharmacology/toxicology perspective.

### 1.1.2 Additional Non Clinical Recommendations

None

### 1.1.3 Labeling

The following recommendations are being proposed for the nonclinical sections of the label. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling in Table 1 are in red or strikeout font.

The nonclinical sections of the proposed label for Oxymorphone (b) (4) ER (OM (b) (4) ER) are identical to the Applicant's current draft of the PLR conversion for OPANA ER. The reviewer's proposed changes to the label for this product are the same for the PLR conversion for OPANA ER. The current version of the OPANA ER label (approved February 29, 2008) and the proposed version for OM (b) (4) ER submitted with this NDA use several different human doses of oxymorphone for nonclinical exposure comparisons. These include 40 mg every 12 h, (b) (4) 260 mg/day. In order to avoid confusion for the prescribing physician, the human dose used for all nonclinical sections will be 40 mg every 12 h (80 mg/day). This dose was selected as the comparison dose for the nonclinical data because it is using the highest available strength for both the OM (b) (4) ER and OPANA ER products dosed every 12 h as indicated in the labeling. Comparisons will be made on a body surface area basis. An exception to the human/animal dose comparison of 40 mg every 12 h based on body surface area will be the AUC comparisons in the carcinogenicity section. In the current draft of the label, the human dose of 260 mg oxymorphone is used in the exposure comparison (AUC) for the mouse and rat carcinogenicity studies. This dose was selected during the original NDA labeling review of OPANA ER because it was the highest dose used in the clinical trials with AUC values available (refer to NDA 21-610 review by Dr. Mamata De). The oxymorphone carcinogenicity studies for the OPANA ER NDA were the first dedicated opiate carcinogenicity assessments to be included in an opiate label. At the time of writing the original OPANA ER and OPANA IR product labels, it was thought to use the highest human dose with AUC values as a comparison because the population of patients taking oxymorphone chronically would be an opioid tolerant population taking theoretically very high doses. In this labeling review, based on the previous rationale it was decided that the 260 mg oxymorphone human AUC exposure comparison for the mouse and rat carcinogenicity studies should remain.

Refer to Table 1 for the reviewer's edits and rationale for the edits to the version of the label provided by the Applicant.

**Table 1 Labeling Review**

<b><i>Applicant's proposed labeling</i></b>	<b><i>Reviewer's proposed changes</i></b>	<b><i>Rationale for changes</i></b>
<p><i>(from highlights section)</i>  <b>INDICATIONS AND USAGE</b></p> <ul style="list-style-type: none"> <li>TRADEMARK is an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. (1)</li> </ul>	<p><i>(from highlights section)</i>  <b>INDICATIONS AND USAGE</b></p> <ul style="list-style-type: none"> <li>TRADEMARK is an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. (1)</li> </ul>	No changes were made to this section.
<p><b>8 USE IN SPECIFIC POPULATIONS</b>  <b>8.1 Pregnancy</b>  The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of TRADEMARK in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighed against the possible hazards to the mother and the child.</p> <p><b><u>Teratogenic Effects</u></b></p> <p><b><u>Pregnancy Category C</u></b></p> <p>There are no adequate and well-controlled studies of oxymorphone in pregnant women. (b) (4)</p> <p>TRADEMARK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p> <p>Oxymorphone hydrochloride administration did not cause malformations at any doses evaluated during developmental toxicity studies in rats (<math>\leq 25</math> mg/kg/day) or rabbits (<math>\leq 50</math> mg/kg/day). These doses are ~3-fold and ~12-fold the human dose of 40 mg every 12 hours, based on body surface area. There were no developmental effects in rats treated with 5 mg/kg/day or rabbits</p>	<p><b>8 USE IN SPECIFIC POPULATIONS</b>  <b>8.1 Pregnancy</b>  The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of TRADEMARK in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighed against the possible hazards to the mother and the child.</p> <p><b><u>Teratogenic Effects</u></b></p> <p><b><u>Pregnancy Category C</u></b></p> <p>There are no adequate and well-controlled studies of oxymorphone in pregnant women. (b) (4)</p> <p>TRADEMARK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p> <p>Oxymorphone hydrochloride administration did not cause malformations at any doses evaluated during developmental toxicity studies in rats (<math>\leq 25</math> mg/kg/day) or rabbits (<math>\leq 50</math> mg/kg/day). These doses are ~3-fold and ~12-fold the human dose of 40 mg every 12 hours, based on body surface area. There were no developmental effects in rats treated with 5 mg/kg/day or rabbits</p>	<p>(b) (4)</p>

<p>treated with 25 mg/kg/day. Fetal weights were reduced in rats and rabbits given doses of <math>\geq 10</math> mg/kg/day and 50 mg/kg/day, respectively. These doses are <math>\sim 1.2</math>-fold and (b) (4)-fold the human dose of 40 mg every 12 hours based on body surface area, respectively. There were no effects of oxymorphone hydrochloride on intrauterine survival in rats at doses <math>\leq 25</math> mg/kg/day, or rabbits at <math>\leq 50</math> mg/kg/day in these studies (see Non-teratogenic Effects, below). In a study that was conducted prior to the establishment of Good Laboratory Practices (GLP) and not according to current recommended methodology, a single subcutaneous injection of oxymorphone hydrochloride on gestation day 8 was reported to produce malformations in offspring of hamsters that received 15.5-fold the human dose of 40 mg every 12 hours based on body surface area. This dose also produced (b) (4) % maternal lethality.</p>	<p>treated with 25 mg/kg/day. Fetal weights were reduced in rats and rabbits given doses of <math>\geq 10</math> mg/kg/day and 50 mg/kg/day, respectively. These doses are <math>\sim 1.2</math>-fold and (b) (4) 12-fold the human dose of 40 mg every 12 hours based on body surface area, respectively. There were no effects of oxymorphone hydrochloride on intrauterine survival in rats at doses <math>\leq 25</math> mg/kg/day, or rabbits at <math>\leq 50</math> mg/kg/day in these studies (see Non-teratogenic Effects, below). In a study that was conducted prior to the establishment of Good Laboratory Practices (GLP) and not according to current recommended methodology, a single subcutaneous injection of oxymorphone hydrochloride on gestation day 8 was reported to produce malformations in offspring of hamsters that received 15.5-fold the human dose of 40 mg every 12 hours based on body surface area. This dose also produced (b) (4) 20% maternal lethality.</p>	<p>(b) (4)</p>
<p><b><u>Non-teratogenic Effects</u></b></p>	<p><b><u>Non-teratogenic Effects</u></b></p>	<p>(b) (4)</p>
<p>Oxymorphone hydrochloride administration to female rats during gestation in a pre- and postnatal developmental toxicity study reduced mean litter size (18%) at a dose of 25 mg/kg/day, attributed to an increased incidence of stillborn pups. An increase in neonatal death occurred at <math>\geq 5</math> mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated (b) (4) rats given a dose of 25 mg/kg/day. This dose is <math>\sim 3</math>-fold higher than the human dose of 40 mg every 12 hours on a body surface area basis.</p>	<p>Oxymorphone hydrochloride administration to female rats during gestation in a pre- and postnatal developmental toxicity study reduced mean litter size (18%) at a dose of 25 mg/kg/day, attributed to an increased incidence of stillborn pups. An increase in neonatal death occurred at <math>\geq 5</math> mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated female (b) (4) rats given a dose of 25 mg/kg/day. This dose is <math>\sim 3</math>-fold higher than the human dose of 40 mg every 12 hours on a body surface area basis.</p>	<p>(b) (4)</p>
<p>Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence. Neonatal withdrawal may occur. Symptoms usually appear during the first days of life and may include convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning, and increased respiratory rate.</p>	<p>Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence. Neonatal withdrawal may occur. Symptoms usually appear during the first days of life and may include convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning, and increased respiratory rate.</p>	
<p><b>13 NONCLINICAL TOXICOLOGY</b>  <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>  <b>Carcinogenesis</b></p>	<p><b>13 NONCLINICAL TOXICOLOGY</b>  <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>  <b>Carcinogenesis</b></p>	



<p>Long-term studies have been completed to evaluate the carcinogenic potential of oxymorphone in both Sprague-Dawley rats and CD-1 mice. Oxymorphone HCl was administered to Sprague-Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day in male rats was 0.34-fold and at the 25 mg/kg/day dose in female rats was 1.5-fold the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in rats. Oxymorphone was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 150 mg/kg/day dose in mice was 14.5-fold (in males) and 17.3-fold (in females) times the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in mice.</p>	<p>Long-term studies have been completed to evaluate the carcinogenic potential of oxymorphone in both Sprague-Dawley rats and CD-1 mice. Oxymorphone HCl was administered to Sprague-Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day in male rats was 0.34-fold and at the 25 mg/kg/day dose in female rats was 1.5-fold the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in rats. Oxymorphone was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 150 mg/kg/day dose in mice was 14.5-fold (in males) and 17.3-fold (in females) times the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in mice.</p>	
<p><u>Mutagenesis</u> Oxymorphone hydrochloride was not mutagenic when tested in the <i>in vitro</i> bacterial reverse mutation assay (Ames test) at concentrations of <math>\leq 5270</math> <math>\mu\text{g}/\text{plate}</math>, or in an <i>in vitro</i> mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations <math>\leq 5000</math> <math>\mu\text{g}/\text{ml}</math> with or without metabolic activation. Oxymorphone hydrochloride tested positive in both the rat and mouse <i>in vivo</i> micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses <math>\geq 250</math> mg/kg and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after</p>	<p><u>Mutagenesis</u> Oxymorphone hydrochloride was not mutagenic when tested in the <i>in vitro</i> bacterial reverse mutation assay (Ames test) at concentrations of <math>\leq 5270</math> <math>\mu\text{g}/\text{plate}</math>, or in an <i>in vitro</i> mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations <math>\leq 5000</math> <math>\mu\text{g}/\text{ml}</math> with or without metabolic activation. Oxymorphone hydrochloride tested positive in both the rat and mouse <i>in vivo</i> micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses <math>\geq 250</math> mg/kg and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after</p>	

<p>administration of 40 mg/kg oxymorphone.</p> <p><u>Impairment of fertility</u>  Oxymorphone hydrochloride did not affect reproductive function or sperm parameters in male rats at any dose tested (<math>\leq 50</math> mg/kg/day). In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at doses of oxymorphone <math>\geq 10</math> mg/kg/day. The dose of oxymorphone associated with reproductive findings in female rats is 1.2-fold the human dose of 40 mg every 12 hours based on a body surface area. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.</p>	<p>administration of 40 mg/kg oxymorphone.</p> <p><u>Impairment of fertility</u>  Oxymorphone hydrochloride did not affect reproductive function or sperm parameters in male rats at any dose tested (<math>\leq 50</math> mg/kg/day). <b>The highest dose tested is ~6-fold the human dose of 40 mg every 12 hours, based on body surface area.</b> In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at doses of oxymorphone <math>\geq 10</math> mg/kg/day. The dose of oxymorphone associated with reproductive findings in female rats is 1.2-fold the human dose of 40 mg every 12 hours based on a body surface area. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.</p>	<p>The exposure comparison for males was added.</p>
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## 1.2 Brief Discussion of Nonclinical Findings

NDA 201-655 for Oxymorphone HCl (b) (4) ER (Endo Pharmaceuticals) is being submitted via the 505(b)(1) regulatory pathway. Cross-reference is made to the nonclinical pharmacology, ADME, and toxicology information for oxymorphone provided in NDA 21-610 (OPANA ER) which is also owned by Endo Pharmaceuticals. The applicant also references the rat and mouse carcinogenicity studies submitted to IND 56,919 (Oxymorphone HCl (b) (4); Endo Pharmaceuticals). These studies are described in the current versions of the both OPANA IR and OPANA ER labels and will be described in the label for this product.

No nonclinical studies were conducted for this NDA. There are no unique nonclinical issues with this product as compared to OPANA ER or other approved oxymorphone products. The impurities/degradants are controlled at acceptable levels in both the drug substance and drug product. The excipients used in this formulation can be found in previously approved products and do not pose any unique toxicologic concerns. There are no outstanding pharmacology or toxicology issues for NDA 201-655 and the recommendation from the Pharmacology/Toxicology perspective is approval.

## 2 Drug Information

### 2.1 Drug

Oxymorphone Hydrochloride (b) (4) Extended-Release Tablet

### 2.1.1 CAS Registry Number

357-07-03

### 2.1.2 Generic Name

Oxymorphone hydrochloride

### 2.1.3 Code Name

EN3288

### 2.1.4 Chemical Name

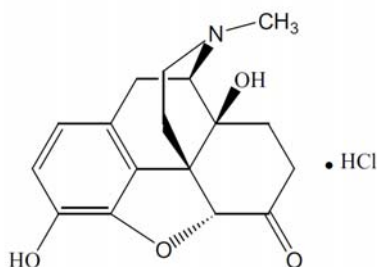
4,5  $\alpha$ -epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride

### 2.1.5 Molecular Formula/Molecular Weight

C<sub>17</sub>H<sub>19</sub>NO<sub>4</sub>·HCl; MW= 337.80

### 2.1.6 Structure

**Figure 1 Structure of Oxymorphone HCl**



### 2.1.7 Pharmacologic class

Opioid agonist

## 2.2 Relevant IND/s, NDA/s, and DMF/s

**Table 2 Relevant IND/s, NDA/s and DMF/s**

IND/NDA/DMF	drug/compound	sponsor	division	status
IND 104,250	Oxymorphone (b) (4) ER	Endo	DAAP	active
NDA 21-611	OPANA IR	Endo	DAAP	approved
NDA 22-610	OPANA ER	Endo	DAAP	approved

IND 58,602	OPANA IR	Endo	DAAP	active
IND 56,919	Oxymorphone (b) (4)	Endo	DAAP	active
DMF (b) (4)	Oxymorphone HCl	(b) (4)	ONDQA	reviewed by Dr. Julia Pinto (2010)

## 2.3 Clinical Formulation

The Oxymorphone HCl (b) (4) Extended-Release tablet (OM (b) (4) ER) is an extended release oxymorphone HCl (OM) formulation with properties purported by the applicant to reduce accidental misuse (i.e. by breakage or crushing) and to deter certain methods of intended abuse (i.e. intentional crushing for snorting or injection).

The tablet is produced by (b) (4)

The indication proposed for the OM (b) (4) ER tablet is the relief of moderate to severe pain in adult patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The product will be labeled for twice daily administration and will be available in 5, 7.5, 10, 15, 20, 30, and 40 mg tablets. The amounts of each excipient per 40 mg tablet and at the maximum theoretical daily dose of OM are listed in Table 3. Refer to discussion of the MTDD of OM in Section 2.4. Levels of all excipients in the formulation when the product is used at the MTDD of OM are acceptable; refer to Section 2.3.2 for discussion.

**Table 3 Oxymorphone (b) (4) ER Formulation**

<b><i>Ingredient</i></b>	<b><i>per 40 mg tablet (mg)</i></b>	<b><i>TDI in an opioid tolerant patient* (mg)</i></b>
Polyethylene oxide	(b) (4)	
Hypromellose (b) (4)		
Polyethylene glycol (b) (4)		
α-Tocopherol		
Citric acid, anhydrous		

\*Total daily intake based on the maximum theoretical daily dose (MTDD) of oxymorphone in an opioid tolerant patient of 1 g/day (refer to Section 2.4 for discussion of MTDD)

### 2.3.1 Drug Formulation

See Section 2.3

### 2.3.2 Comments on Novel Excipients

All of the excipients in the OM (b) (4) ER formulation are found in approved drug products and are listed in the FDA Inactive Ingredients Guide (IIG; Table 3). However, two of the excipients in the OM (b) (4) ER drug product will exceed levels in previously approved drugs when the MTDD of OM is consumed. Polyethylene oxide (PEO) is found in OM (b) (4) ER at a total daily dose of (b) (4) when the highest strength tablet is consumed at the MTDD of OM. Polyethylene oxide is found in the FDA approved product OxyContin at a level of (b) (4) when the product is used at the MTDD of oxycodone. Therefore, the levels of PEO in the OM (b) (4) ER product are considered acceptable. The levels of  $\alpha$ -tocopherol (Vitamin E; (b) (4)) in OM (b) (4) ER, when the highest strength tablet is used at the MTDD of OM, exceed the values listed in the IIG. However, the upper safe limit of Vitamin E established by the Food and Nutrition Board of the Institute of Medicine is 1000 mg daily. Therefore, the levels of  $\alpha$ -tocopherol in the OM (b) (4) ER product are considered acceptable.

Levels of all excipients in the formulation of OM (b) (4) ER when used at the MTDD of OM are considered acceptable from the pharmacology/toxicology perspective and do not pose any unique toxicologic concerns.

### 2.3.3 Comments on Impurities/Degradants of Concern

#### Drug Substance Impurities

The applicant is referencing DMF (b) (4) for the OM drug substance. The qualification threshold according to the ICH Q3A (R2) guidance for impurities in the drug substance for a maximum daily dose (MDD) of  $\leq 2$  g/day is 0.15% or 1 mg/day intake, whichever is lower. The applicant has set the specifications for drug substance impurities at NMT (b) (4) unless otherwise noted (Table 4; see discussion of specific exceptions below). For a MDD of (b) (4) of OM with a specification of (b) (4) the TDI of the impurity would be (b) (4), which exceeds the 1 mg/day maximum as stated in ICH Q3A (R2). Although these OM drug substance specifications do not technically meet ICH Q3A (R2) guidelines, several products have been approved by FDA and are currently marketed using the same drug substance DMF. No safety signals have arisen and the proposed drug substance specifications of NMT (b) (4), although slightly exceeding ICH Q3A (R2) thresholds, are considered to be of no toxicologic concern.

**Table 4 Drug Substance Specifications: Oxymorphone HCl**

<b>Impurity</b>	<b>Acceptance Specification</b>	<b>Acceptable?</b>
(b) (4)	(b) (4)	<b>Yes</b>
		<b>Yes</b>
		<b>Yes</b>
		<b>Yes: FDA approved compound</b>
		<b>Yes</b>
		<b>Yes: ICSAS comp tox report</b>

(b) (4)

**Drug Product Impurities/Degradants**

The qualification threshold according to the ICH Q3B (R2) guidance for impurities/degradants in the drug product for the MDD of the drug substance administered per day between (b) (4) (MDD of OM is (b) (4)) is (b) (4) or (b) (4) TDI, whichever is lower. The Applicant has set the stability specifications for impurities/degradation products at (b) (4) and no further qualification will be necessary (Table 5).

**Table 5 Drug Product Specifications: Oxymorphone HCl (b) (4) ER**

<b>Impurity</b>	<b>Acceptance Criteria</b>	<b>Acceptable?</b>
(b) (4)		<b>Yes</b>
		<b>Yes</b>
		<b>Yes</b>
		<b>Yes</b>

**2.4 Proposed Clinical Population and Dosing Regimen**

The Oxymorphone HCl (b) (4) Extended-Release tablet (OM (b) (4) ER) is proposed to be indicated for the relief of moderate to severe pain in adult patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The product will be labeled to be administered twice daily and will be available in 5, 7.5, 10, 15, 20, 30, and 40 mg tablets.

**Determination of the maximum theoretical daily dose (MTDD) of oxymorphone**

The maximal dosing information for OM is relevant to this review in that the ICH specifications for impurity levels for the drug substance and the drug product as well as the acceptable levels of total amount of inactive ingredients are based on the total daily dose of the drug substance.

The development of tolerance to the effects of an opioid precludes easily defining a maximum daily dose. The reduced effectiveness as a result of tolerance necessitates

increased dosing in order to maintain the desired therapeutic effect. Therefore, in an opioid tolerant individual, very high daily doses are theoretically possible. Because the dosing is tailored to the individual needs of the patient it not possible to set a maximum daily dose that fits all patients. Based on potency comparisons with morphine, the clinicians in DAAP have determined that a reasonable maximum theoretical daily dose (MTDD) of OM in an opioid tolerant individual is (b) (4).

## **2.5 Regulatory Background**

NDA 201-655 (Endo Pharmaceuticals) is being submitted via the 505(b)(1) regulatory pathway. Cross-reference is made to the nonclinical pharmacology, ADME, and toxicology information for oxymorphone provided in NDA 21-610 (OPANA ER) which is also owned by Endo Pharmaceuticals. The applicant also references the rat and mouse carcinogenicity studies submitted to IND 56,919 (OPANA ER). These studies are described in the current versions of the both OPANA IR and OPANA ER labels. No nonclinical studies were conducted for this NDA.

## **3 Studies Submitted**

### **3.1 Studies Reviewed**

No studies were submitted with this NDA.

### **3.2 Studies Not Reviewed**

### **3.3 Previous Reviews Referenced**

Refer to the combined pharmacology toxicology review for OPANA IR and OPANA ER (NDAs 21-611 and 21-610, respectively) by Dr. R. Daniel Mellon dated October 15 2003 for the first cycle review and by Dr. Mamata De dated June 16, 2006 for the second cycle review. The rat and mouse carcinogenicity studies were submitted to IND 56,919 and were reviewed in the NDA review mentioned above by Dr. Mamata De.

## **4 Pharmacology**

Oxymorphone is a semi-synthetic mu opioid receptor agonist with a long history of safe use. The pharmacology has been well characterized and is described in the NDA review of OPANA ER (22-610). The applicant owns and is cross-referencing NDA 22-610 to support approval of this NDA. No new pharmacology studies were submitted with this NDA.

#### **4.1 Primary Pharmacology**

#### **4.2 Secondary Pharmacology**

#### **4.3 Safety Pharmacology**

### **5 Pharmacokinetics/ADME/Toxicokinetics**

No new studies were submitted. Refer to review of NDA 22-610 for discussion.

#### **5.1 PK/ADME**

#### **5.2 Toxicokinetics**

### **6 General Toxicology**

No new studies were submitted. Refer to review of NDA 22-610 for discussion.

#### **6.1 Single-Dose Toxicity**

#### **6.2 Repeat-Dose Toxicity**

### **7 Genetic Toxicology**

No new studies were submitted. Refer to review of NDA 22-610 for discussion.

### **8 Carcinogenicity**

No new studies were submitted. Refer to review of NDA 22-610 for discussion.

### **9 Reproductive and Developmental Toxicology**

No new studies were submitted. Refer to review of NDA 22-610 for discussion.



### **9.1 Fertility and Early Embryonic Development**

### **9.2 Embryonic Fetal Development**

### **9.3 Prenatal and Postnatal Development**

## **10 Special Toxicology Studies**

No new studies were submitted.

## **11 Integrated Summary and Safety Evaluation**

There are no unique nonclinical issues with this product as compared to OPANA ER or other approved oxymorphone products. The impurities/degradants are controlled at acceptable levels in both the drug substance and drug product. The excipients used in this formulation can be found in previously approved products and do not pose any unique toxicologic concerns. There are no outstanding pharmacology/toxicology issues with NDA 201-655 and the recommendation from the Pharmacology/Toxicology perspective is approval.

## **12 Appendix/Attachments**

### ***Appendix 1***

(b) (4)



(b) (4)



## Reference List

Ashby J, Tennant RW (1988) Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. *Mutat Res* 204:17-115.

Eder E, Hoffman C, Bastian H, Deininger C, Scheckenbach S (1990) Molecular mechanisms of DNA damage initiated by alpha, beta-unsaturated carbonyl compounds as criteria for genotoxicity and mutagenicity. *Environ Health Perspect* 88:99-106.

Eder E, Scheckenbach S, Deininger C, Hoffman C (1993) The possible role of alpha, beta-unsaturated carbonyl compounds in mutagenesis and carcinogenesis. *Toxicol Lett* 67:87-103.

Geber WF, Schramm LC (1975) Congenital malformations of the central nervous system produced by narcotic analgesics in the hamster. *Am J Obstet Gynecol* 123:705-713.

Sawatari K, Nakanishi Y, Matsushima T (2001) Relationships between chemical structures and mutagenicity: a preliminary survey for a database of mutagenicity test results of new work place chemicals. *Ind Health* 39:341-345.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201655	ORIG-1	ENDO PHARMACEUTICA LS INC	Oxymorphone HCl (b) (4) extended-release tablet

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/s/

ELIZABETH BOLAN  
09/07/2010

RICHARD D MELLON  
09/07/2010  
I concur.

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 201-655    Applicant: Endo Pharmaceuticals    Stamp Date: July 7, 2010**

**Drug Name: Oxymorphone    NDA/BLA Type: 505(b)(1)**  
(b) (4) **ER (Oxymorphone HCl)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	X		Refer to CSS review
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION  
FILEABLE? \_\_\_\_ Yes \_\_\_\_**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**No issues were identified during the filing review.**

Elizabeth A. Bolan, Ph.D.  
Reviewing Pharmacologist

August 10, 2010  
Date

Team Leader/Supervisor

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201655	ORIG-1	ENDO PHARMACEUTICA LS INC	Oxymorphone HCl (b) (4) extended-release tablet

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

/s/

ELIZABETH BOLAN  
08/16/2010

RICHARD D MELLON  
08/16/2010