

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201655Orig1s000

MEDICAL REVIEW(S)



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Summary Review for Regulatory Action

Date	January 7, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia and Analgesia Products
Subject	Division Director Summary Review
NDA #	201655
Applicant Name	Endo Pharmaceuticals
Date of Submission	July 7, 2010
PDUFA Goal Date	January 7, 2011
Proprietary Name / Established (USAN) Name	(b) (4) Oxymorphone HCl extended-release tablets
Dosage Forms / Strength	Extended-release tablets 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg
Proposed Indication	For the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time
Action:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Clinical Review	N/A
Statistical Review (supporting CSS)	Ling Chen, Ph.D.; Stella Machado, Ph.D.
Preclinical Review	Elizabeth Bolan, Ph.D.; Dan Mellon, Ph.D.
CMC Review	Craig Bertha, Ph.D., Prasad Peri, Ph.D.
Microbiology Review	James McVey, Ph.D.; Steven Langille, Ph.D.
Clinical Pharmacology Review	Srikanth Nallani, Ph.D., Suresh Doddapaneni, Ph.D.
Biopharmaceutics	Sandra Suarez Sharp, Ph.D.; Patrick Marroum, Ph.D.
DSI	John Kadavil, Ph.D.; Sam Haider, Ph.D.; Martin Yau, Ph.D.
CDTL Review	Ellen Fields, M.D., M.P.H.
OSE/DMEPA	Tara Turner, Pharm.D.; Jibril Abdus-Samad, Pharm.D.; Todd Bridges, R.Ph.; Zachary Oleszczuk, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DRISK	Steve Morin, R.N., B.S.N., O.C.N.; Barbara Fuller, R.N., M.S.N., Sharon Mills, B.S.N., R.N., C.C.R.P.; Marcia Britt, Ph.D.; Agnes Plante, B.S.N., R.N.; Megan Moncur, M.S.; Claudia Karwoski, Pharm.D.
OSE/DEPI	Rajdeep Gill, Pharm.D.; Laura Governale, Pharm.D., M.B.A.
DDMAC	Twyla Thompson; Mathilda Fienkeng
Controlled Substance Staff	James Tolliver, Ph.D.; Silvia Calderon, Ph.D.; Michael Klein, Ph.D.

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader

1. Introduction

Endo Pharmaceuticals has submitted this application for a reformulated version of their approved oxymorphone ER product, Opana ER. This new formulation, developed with their partner Grünenthal GmbH, [REDACTED] ^{(b) (4)} and to thereby reduce accidental misuse and deter certain specific methods of abuse. The support for the efficacy and safety of this new product is intended to be based entirely on bioequivalence to the previously approved product. The new formulation will be dosed on the same schedule as the old formulation and will be available in the same dosage strengths.

2. Background

Based on our experience with a number of different purportedly abuse-deterrent opioid analgesic products, some approved and others still in development, and on the comments and conclusions on this topic received from the members of a joint meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees in October of last year, we have determined that any reasonable, well-documented, even incremental change in the formulation of an abusable opioid that will possibly deter misuse and abuse is a positive step in dealing with the public health crisis of prescription opioid abuse in the United States. Both the members of the advisory committee and the Agency have also concluded that the available databases for determining whether these products actually reduce abuse in the community are inadequate to track changes over time at this point [REDACTED] (b) (4)

[REDACTED] However, in order to provide as much information as possible regarding the advantages of these products to prescribers and patients, the labels will incorporate language describing [REDACTED] (b) (4) of the new formulation and the routes of abuse that they are intended to deter.

Endo's product has demonstrated a minimal improvement in resistance to tampering by crushing, thereby limiting the likelihood of abuse by ingestion and by insufflation (snorting) to some degree. [REDACTED] (b) (4)

[REDACTED] cut [REDACTED] (b) (4)
[REDACTED] (b) (4) rendering it readily abusable by ingestion and intravenous injection, and possibly still by insufflation, although they have not tested whether the [REDACTED] (b) (4) tablets can be snorted. Of more concern, when chewed [REDACTED] (b) (4)
[REDACTED] (b) (4), the new formulation essentially dose dumps like an immediate-release formulation. While the label and MedGuide would certainly carry warnings against chewing, some concern exists that any language in the label noting the reduced crushability of this formulation could be misleading and result in health care practitioners or patients thinking that it is safer than the old formulation, and that it is safe to chew the product; or that it is safe to give the new product to a cognitively impaired patient who may chew the product if not adequately supervised.

This application's basis for establishing the safety and efficacy of the new formulation is entirely dependent upon two bioequivalence (BE) studies comparing the new and old formulations. Based on an inspection of the CRO site that performed those studies, the Division of Scientific Investigation (DSI) has determined that there were significant procedural flaws in the performance of Study EN3288-103 and they have recommended that the study not be accepted for use in this application. Study EN3288-103 evaluated the 40 mg strength tablets of [REDACTED] (b) (4) compared to the 40 mg strength tablets of Opana ER in normal volunteers under fasting conditions and naltrexone blockade. DSI issued a 483 to the CRO on December 9, 2010, and DSI completed their review and final recommendations to the Division on December 20, 2010. Endo was notified of this finding by the division via teleconference on

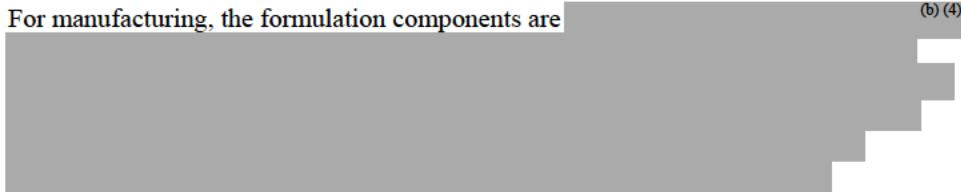
December 27, 2010, and a Discipline Review Letter was sent to the sponsor on December 28, 2010, documenting these concerns and their possible impact on approvability. The CRO sent in a response to the 483 comments on December 29, 2010, and the response has been reviewed by DSI. Based on that review, DSI has maintained their recommendation to the division that we not use Study EN3288-103 in our assessment of the application's approvability. While Study EN3288-105, a BE study of the 5 mg tablets, also demonstrated bioequivalence to the old formulation, the Office of Clinical Pharmacology cannot make a determination of bioequivalence for the higher strength tablets based on these findings as, in a BE study, the intent is to compare the formulations for rate and extent of drug absorption after release from a given type of formulation, and this is best done with the highest strength as, over a prolonged period of time, C_{max} and AUC can be acquired with due consideration for analytical methods, duration of sampling, and duration of formulation passage in the gastrointestinal tract. Often the lowest strength formulations have plasma levels detectable for a shorter period of time, depending on the sensitivity of the analytical method.

In addition, the DSI findings raise systemic concerns about the studies performed at the CRO in question.

3. CMC

The following has been reproduced from page 8 of Dr. Bertha's review:

For manufacturing, the formulation components are [REDACTED] (b) (4)



I concur with the CMC review team that there are no outstanding issues that would impact approvability. The Office of Compliance issued an overall recommendation of Acceptable in regard to the facilities inspections on November 15, 2010.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data was submitted with this application. The excipients used in the new formulation have either been used in approved products or have been found to be acceptable by the review team. I concur with the pharmacology/toxicology review team that there are no outstanding issues that would impact approvability.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology program for [REDACTED] ^{(b)(4)} has been reproduced from pages 3 through 8 of Dr. Fields' review:

Six pharmacokinetic studies were conducted in healthy volunteers to support the efficacy, safety [REDACTED] ^{(b)(4)} [REDACTED] tablets as shown in the tables below from Dr. Nallani's review.

Table 1: Studies establishing bioequivalence of [REDACTED] ^{(b)(4)} to Opana ER

Study # EN3288-103: BE study comparing [REDACTED] ^{(b)(4)} 40 mg compared to OPANA ER 40 mg in healthy subjects under fasting state and naltrexone blockade.
Study # EN3288-104: BE study comparing [REDACTED] ^{(b)(4)} 40 mg compared to OPANA ER 40 mg in healthy subjects under fed state and naltrexone blockade.
Study # EN3288-105: BE study comparing [REDACTED] ^{(b)(4)} 5 mg compared to OPANA ER 5 mg in healthy subjects under fasting and naltrexone blockade.

Table 2: PK studies conducted to evaluate dose dumping of [REDACTED] ^{(b)(4)} after improper use

Study # EN3288-107: Alcohol interaction study assessing relative bioavailability of [REDACTED] ^{(b)(4)} 40 mg taken with or without an alcoholic beverage and naltrexone blockade.
Study # EN3288-108: Relative bioavailability study comparing [REDACTED] ^{(b)(4)} 40 mg taken intact and after physical tampering (cutting, crushing and grinding) and naltrexone blockade.
Study # EN3288-109: Relative bioavailability and drug-liking study comparing [REDACTED] ^{(b)(4)} 40 mg taken intact and after chewing without naltrexone blockade.

Additional in vitro studies were performed by the Applicant to address if different methods of tampering with controlled-release products known to drug addicts would defeat the extended-release properties of [REDACTED] ^{(b)(4)}. These studies were reviewed by Drs Sharp and Tolliver and will be discussed later in this review.

Bioequivalence of [REDACTED] ^{(b)(4)} to Opana ER was established with the highest dose, 40mg, and the lowest dose, 5mg, under fasting conditions. The adequacy of the in vitro dissolution profiles submitted in support of the biowaiver for the intermediate strengths was reviewed by Dr. Sharp and found acceptable. The table below from Sr. Nallani's review shows the results of the BE studies. Note that [REDACTED] ^{(b)(4)} 40mg is also bioequivalent to Opana ER 40mg under fed conditions.

Table 3: Summary Table of BE analyses of [b] compared to Opana ER

Parameter	Geometric Least Squares Means		Ratio of Means	90% Confidence Interval
	EN3288	OPANA ER		
EN3288-103: Single 40 mg Oral Doses to Fasted Healthy Subjects*				
Cmax (ng/mL)				(b) (4)
AUC0-t (ng•h/mL)				
EN3288-104: Single 40 mg Oral Doses to Healthy Subjects with a High-Fat Meal				
Cmax (ng/mL)	5.24	5.55	0.94	0.88-1.02
AUC0-t (ng•h/mL)	47.10	48.43	0.97	0.93-1.02
EN3288-105: Single 5 mg Oral Doses to Fasted Healthy Subjects				
Cmax (ng/mL)	0.352	0.360	0.98	0.93-1.03
AUC0-t (ng•h/mL)	5.04	4.82	1.05	1.01-1.09

Previously, during the review of OPANA ER in NDA 21-610, the Clinical Pharmacology reviewer noted a large food effect, such that the mean oxymorphone Cmax in the fed state was about 52% higher than the Cmax in fasted state. Since [b] and OPANA ER are bioequivalent under fasting and fed conditions, it can be assumed that [b] has the same degree of food effect as OPANA ER. Current dosing recommendations for OPANA ER indicate that the tablet should be dosed at least one hour prior to or two hours after eating. The same dosing recommendation will apply to [b]

Dr. Nallani discussed the extended-release profile of [b] under normal and improper use in his review. The Applicant conducted a study to evaluate alcohol drug interaction effects of consuming 20% or 40% alcohol on the pharmacokinetic profile of [b]. The results indicated that similar to Opana ER, administration of beverages containing alcohol (20% and 40%) resulted in significant increase in peak plasma levels. On average, oxymorphone Cmax increased with the amount of ethanol consumed and was 1.14-fold and 1.80-fold higher with 20% and 40% ethanol, respectively. Noteworthy is the fact that in certain individuals maximum fold change in Cmax up to 2.5-fold or 5.5-fold were noted in 20% or 40% alcohol treatment groups compared to [b] alone.

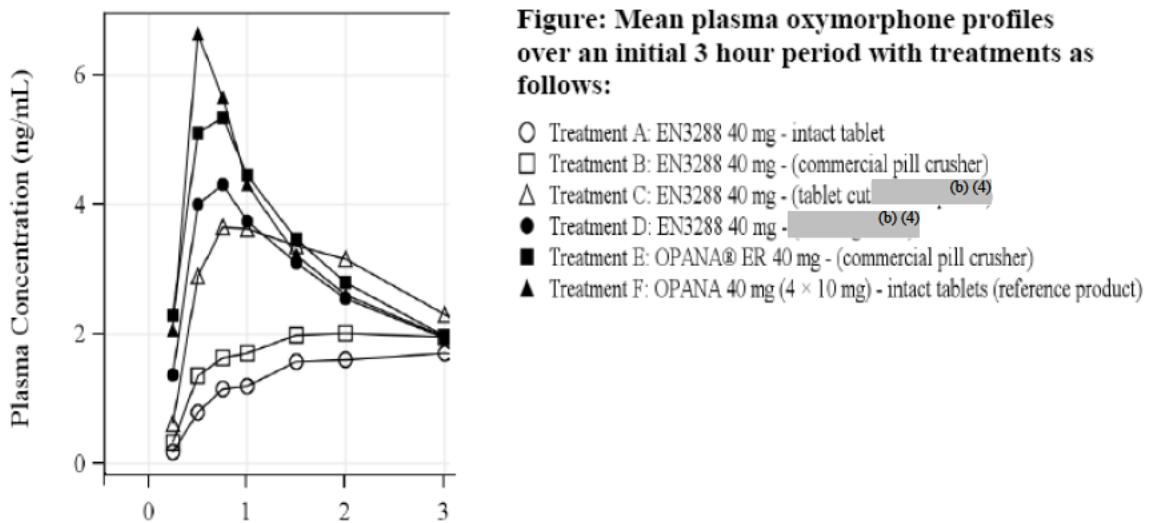
[b] and OPANA ER are similar in their susceptibility to alcohol-related drug interaction. Interestingly, this interaction is not due to the failure of the extended-release characteristics of the formulation but is probably due to the alcohol effect on the absorption of oxymorphone itself. For both OPANA ER and [b] in vitro dissolution studies have demonstrated that these products do not release oxymorphone more rapidly in dissolution media containing alcohol.

A study was conducted by the Applicant to evaluate dose dumping of oxymorphone under conditions of accidental or intentional misuse by breaking and/or crushing with different methods. It was an open-label, randomized, 6-sequence, 6-period crossover design with subjects randomized to the following treatments:

- A EN3288 40 mg – intact tablet
- B EN3288 40 mg – tablet tampered with a commercial pill crusher
- C EN3288 40 mg – tablet cut [REDACTED] (b) (4)
- D EN3288 40 mg – tablet tampered [REDACTED] (b) (4)
- E OPANA ER 40 mg – tablet tampered with a commercial pill crusher
- F OPANA 40 mg (4×10 mg) – intact tablets

The Applicant compared BE of [REDACTED] (b) (4) following physical manipulation (B, C, and D) with Treatment A (intact ER tablets) or Treatment F (40mg IR tablets). Since the goal of this study is to understand whether the extended-release product can withstand physical tampering, PK results from an intact extended-release product is the more appropriate reference. Using intact [REDACTED] (b) (4) as reference, peak plasma levels of oxymorphone failed bioequivalence and were significantly higher when [REDACTED] (b) (4) was consumed following grinding and cutting indicating the loss of extended-release characteristics. However, the data indicates that [REDACTED] (b) (4) resists physical crushing forces noted using a pill crusher (Treatment B) as demonstrated by bioequivalence to intact [REDACTED] (b) (4) with respect to Cmax. In terms of individual data, fold increases in Cmax as high as 4-fold were noted with cutting or grinding the tablet. The following figure from Dr. Nallani's review illustrates the mean plasma oxymorphone profiles for the treatment groups.

Figure 1



The Applicant also conducted a study to evaluate the effect of mastication/chewing on the bioavailability of [REDACTED] (b) (4) 40mg. No specific instructions were given to the study subjects regarding the rate or duration of chewing; they were instructed to completely and carefully chew the tablet for as long as possible. When compared to an intact [REDACTED] (b) (4) tablet, there was a 2.2-fold increase in Cmax when [REDACTED] (b) (4) is consumed after chewing. In terms of individual data, up to 6-fold increases in Cmax were noted when [REDACTED] (b) (4) was consumed after chewing.

Below are conclusions of the Clinical Pharmacology review team as stated in Dr. Nallani's review.

Overall Conclusions:

1. (b) (4) 40 mg is bioequivalent to OPANA ER under fasted and fed conditions. At the time of writing this review, inspection report from DSI of study EN3288-103 is pending.
2. (b) (4) 5 mg is bioequivalent to OPANA ER under fasted condition.
3. Similar to OPANA ER, alcohol-related interaction results in high peak plasma levels.
4. Although (b) (4) seems to resist crushing by pill crusher, it is susceptible to defeat of extended-release characteristics by other methods of physical manipulation. Cutting and grinding (b) (4) resulted in a significant increase in peak plasma levels compared to intact product.
5. As demonstrated by significant increase in peak plasma levels compared to intact product, extended-release characteristics of (b) (4) were defeated when chewed and consumed.

The ONDQA-Biopharmaceutics team reviewed the dissolution methods and specification, the biowaiver request for intermediate doses based on the dissolution profile comparisons, and the in vitro alcohol interaction study.

Dr. Sharp noted in her review that the dissolution method and proposed specifications for all strengths of the (b) (4) tablets are acceptable. The dissolution profiles of all strengths in three different media were determined, and were similar. Therefore the waiver request of the in vivo BE requirements for the intermediate tablet strengths between 5mg and 40mg was granted.

When 40% ethanol was added to the dissolution media, dissolution rates of the 40mg tablets were slower, and there was no change in dissolution rates when 5% ethanol was added. These results are in contrast to the in vivo alcohol interaction study discussed earlier in this section.

Several in vitro studies were conducted to assess the tamper-resistant characteristics of (b) (4). The results of these studies are discussed in the review completed by the Controlled Substance Staff. However, Dr. Sharp notes in her review that (b) (4) does not show good resistance to tampering employed by recreational or experienced abusers, as evidenced by a 60% increase in the dissolution in one hour for tablets (b) (4) compared to intact tablets.

Upon receiving the final recommendation from DSI, the Clinical Pharmacology team reassessed their own recommendations and filed an amendment to their review. The following has been reproduced from page 2 of that amended review written by Dr. Nallani:

Based on the deficiencies identified in the DSI review, the BE study EN3288-103 data cannot be accepted. The following deficiencies and remedial actions to address the

deficiencies from a clinical pharmacology perspective should be conveyed to Endo Pharmaceuticals:

An audit performed by the Agency of the bioequivalence study EN3288-103 identified deficiencies in the methods used at the analytical site. Because of these deficiencies, the bioequivalence study cannot be relied upon to establish bioequivalence of your proposed drug product to the reference product.

This deficiency may be addressed by doing the following:

Provided adequate samples are available, reanalyze blood samples collected in bioequivalence study EN3288-103 and submit data establishing bioequivalence of (b) (4) 40 mg tablets with OPANA ER 40 mg tablets. Ensure that the inspectional findings identified in Agency's audit of study EN3288-103 are properly addressed in the reanalysis of blood samples.

OR

Conduct another pharmacokinetic study and establish bioequivalence of (b) (4) 40 mg tablets with OPANA ER 40 mg tablets under fasting conditions using adequately validated analytical methodology.

6. Clinical Microbiology

There are no clinical microbiology concerns for this application.

7. Clinical/Statistical-Efficacy

No efficacy studies were submitted in this application.

8. Safety

The following summary of the safety data submitted in this application has been reproduced from page 8 of Dr. Fields' review:

The Applicant submitted a Summary of Clinical Safety which included safety data from 240 subjects who received study drug in the pharmacokinetic and tampering studies. In six PK studies, subjects received naltrexone blockade, so the interpretation of the safety data in these studies is limited, as opioid associated adverse events would be blocked, and naltrexone could be the cause of the AEs...

Overall, adverse events reported with EN3288 were not different from those reported for OPANA ER. No deaths were reported during the development program, and there were no SAEs reported in subjects receiving any formulation of oxymorphone. The most frequently occurring events related to EN3288 were vomiting, nausea, dizziness, abdominal pain, and headache, all of which have been reported in the Opana ER label. No new safety signals were detected in the Applicant's studies.

9. Advisory Committee Meeting

This application was not taken to an advisory committee meeting as there were no unusual concerns regarding the efficacy or safety of this reformulated opioid product.

10. Pediatrics

Pediatric studies were not required for this application as a new formulation of an approved drug is not one of the types of applications requiring pediatric data under the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

The following summary of the concerns regarding Study EN288-103 has been reproduced from page 9 of Dr. Fields' review:

Division of Scientific Investigation (DSI) Consult

DSI was consulted in order to inspect the study site that conducted Study EN288-103. An open-label, randomized, single dose, four-period, replicate, crossover study to determine the bioequivalence of EN3288 (Oxymorphone HCl extended-release [REDACTED] (b)(4) formulation) 40 mg compared to OPANA ER (Oxymorphone HCl extended-release) 40 mg in healthy subjects under fasted conditions.

The clinical portion of Study EN3288-103 was conducted at SeaView Research, Inc., Miami, FL. The analytical portion was conducted at [REDACTED] (b)(4). [REDACTED] (b)(4) was also the subject of a complaint received by the Agency in 2009 [REDACTED] (b)(4).

This inspection served as a follow-up to an initial inspection that was conducted in response to the complaint. The site was issued a Form FDA 483 citing the infractions, and the Agency has not yet received a response. [REDACTED]

Details regarding the inspection report are found in the review completed by DSI. [REDACTED] (b)(4)

(b)(4)

10

Division Director's Review and Summary Basis for Complete Response Action

NDA 201655

(b)(4)

January 7, 2011

This is an approvability issue, since this study is one of two key studies establishing bioequivalence with Opana ER. If the firm responds acceptably to the DSI findings within the time period allotted by DSI, these inspection results may not preclude approval, however if not, this NDA will not be approved.

As noted in Section 2, the CRO sent in a response to the 483 comments on December 29, 2010, and that response was reviewed by DSI. Based on their review, DSI retained their recommendation to the division that we not use Study EN3288-103 in our assessment of the application's approvability.

The following conclusions and recommendations from the CSS team have been reproduced from pages 2 through 4 of Dr. Tolliver's review:

2. CONCLUSIONS

We reviewed the *in vitro* manipulation and chemical extraction studies, a clinical pharmacokinetic (bioavailability) study (EN3288-108), human abuse potential studies (EN3288-109), and two bench top attractiveness studies (EN3288-901 and EN3288-902), and have the following conclusions regarding [REDACTED] (b)(4) tablets.

- [REDACTED] (b)(4) provides limited resistance to physical and chemical manipulation for abuse. [REDACTED] (b)(4) extended release mechanism can be overcome by cutting, chewing, or grinding. Intake of [REDACTED] (b)(4) with food or alcohol increases blood levels of oxymorphone. [REDACTED] (b)(4) tablets provide some resistance to crushing [REDACTED] (b)(4)
- The Sponsor did not conduct studies to demonstrate that [REDACTED] (b)(4) tablets can [REDACTED] (b)(4) the difficulty in crushing [REDACTED] (b)(4) tablets [REDACTED] (b)(4) as observed in the *in vitro* studies makes it less likely that, relative to OPANA ER, individuals will intranasally abuse [REDACTED] (b)(4) manipulated using these tools. The bench top study (EN3288-902) demonstrated the difficulty in forming an intranasal preparation with [REDACTED] (b)(4). However, the *in vitro* studies and study EN3288-902 did not address the grinding of [REDACTED] (b)(4) tablets for possible abuse by intranasal administration.
- [REDACTED] (b)(4) tablets are more difficult to cut than are OPANA ER tablets. [REDACTED] (b)(4) Revopan tablets can be cut [REDACTED] (b)(4) compromising the extended release properties of the product.
- An *in vitro* study conducted by the Sponsor shows that it might be easier to prepare a solution for injection when using [REDACTED] (b)(4) than when using OPANA ER. Exposure of a crushed Revopan 40 mg tablet [REDACTED] (b)(4) of the label claim of extracted oxymorphone HCl. However, the bench top manipulation study, Study EN3288-901, showed that both formulations behaved similarly.
- Grinding the [REDACTED] (b)(4) tablets severely compromises the controlled release of oxymorphone HCl, as demonstrated by the high percentages of label claim of oxymorphone HCl [REDACTED] (b)(4). These percentages of label claim [REDACTED] (b)(4) represent extraction levels ranging from [REDACTED] (b)(4) of oxymorphone. Considering that at

equianalgesic doses, oral oxymorphone is [REDACTED] (b) (4) more potent than oral oxycodone when physiological opioid effects (miosis, hypotension, analgesia) are compared, the extracted amounts of oxymorphone are equivalent in its opioid effects of analgesia, miosis, and respiratory depression to [REDACTED] (b) (4) of oral oxycodone respectively.

- [REDACTED] (b) (4) manipulated [REDACTED] (b) (4) tablets or OPANA ER tablets might be difficult, [REDACTED] (b) (4) [REDACTED] (b) (4)
- Clinical abuse liability study EN3288-109 demonstrates that mastication of [REDACTED] (b) (4) 40 mg tablets compromises the controlled release mechanism of [REDACTED] (b) (4)
- Based on the results of pharmacokinetic study EN3288-108 and abuse liability study EN3288-109, it is likely that the ingestion of a [REDACTED] (b) (4) 40 mg tablet cut [REDACTED] (b) (4) will produce substantial and statistically significant subjective reinforcing effects above those produced by the ingestion of intact [REDACTED] (b) (4) 40 mg tablets. In addition, food increases the absorption of oxymorphone, thus increasing the likeability of oxymorphone containing products, including [REDACTED] (b) (4)

3. RECOMMENDATIONS

Based on our review of the relevant studies concerning [REDACTED] (b) (4) Tablets submitted under NDA 201,655 and the above conclusions, we recommend the following:

- The product label not include language asserting that [REDACTED] (b) (4) provides resistance to crushing, [REDACTED] (b) (4)
- Conduct a study to determine if ground [REDACTED] (b) (4) could be administered intranasally, if such a study can be conducted safely. This study is relevant considering that the intranasal route seems to be the most prominent route of abuse of OPANA ER, followed by the oral and intravenous routes as reported by adult individuals (18 years or older) entering treatment (Addiction Severity Index-Multimedia Version (ASI-MV) 2009- Data presented at the FDA joint meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee held October 21-22, 2010 in Gaithersburg, Maryland).

12. Labeling

The review team has provided preliminary recommendations regarding changes to the applicant's proposed labeling. However, final labeling discussions will not occur until the applicant addresses the concerns raised during this review cycle in a resubmission.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
 - Complete Response
- Risk Benefit Assessment

While the applicant has provided data that support the bioequivalence of their reformulated oxymorphone product to Opana ER, the data on the higher-strength tablets were obtained in a study that has been found to be unacceptable upon inspection and review by DSI. Therefore, until the sponsor has either resolved the concerns raised by that review or completed a new BE study, the application cannot be approved.

Additional concerns have been raised regarding the (b) (4) tamper-resistant features of this product's formulation. While some resistance to crushing (b) (4) is inherent in this new formulation, the product can still be (b) (4) cut or chewed to provide rapid release of oxymorphone. It may provide an incremental improvement in tamper resistance for those wishing to snort the drug, and a similarly incremental improvement in preventing overdosage in a patient who attempts to crush the pills in spite of the warnings or when a health care practitioner overlooks the labeled admonition not to crush the pills when administering the product to a patient. However, the product can be (b) (4) cut (b) (4)

(b) (4) Perhaps most importantly, after chewing (b) (4) the product acts like an immediate-release oxymorphone pill and this places certain patient populations, particularly the elderly and/or cognitively impaired, at high risk of overdose. While the latter risk can probably be addressed with adequate warnings in product label, we are concerned that any reference to the product's incremental improvement in tamper resistance could be misleading to health care practitioners and patients, considering the risks noted above. (b) (4)

- Required Postmarketing Risk Evaluation and Mitigation Strategy

As a member of the class of long-acting and extended-release opioid analgesic drug products, (b) (4) is required to have a REMS consistent with the approved class-wide REMS for these products. As with the other approved products in this class, we have accepted an interim REMS while the Agency finalizes our criteria for the class REMS. The company has submitted an interim REMS that is consistent with the requirements set forth by the Agency and with their approved Opana ER product's interim REMS. It consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

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

/s/

BOB A RAPPAPORT
01/07/2011

Cross-Discipline Team Leader Review

Date	December 22, 2010
From	Ellen Fields, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	201655
Applicant	Endo Pharmaceuticals
Date of Submission	July 7, 2010
PDUFA Goal Date	January 7, 2011
Proprietary Name / Established (USAN) names	(b) (4) Oxymorphone HCl extended-release tablets
Dosage forms / Strength	Extended-release tablets/ 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg
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Recommended:	Complete Response

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CMC Reviews	Craig Bertha, Ph.D., Prasad Peri, Ph.D.
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Biopharmaceutics	Sandra Suarez Sharp, Ph.D., Patrick Marroum, Ph.D.
DDMAC	Mathilda Fienkeng
DSI	John Kadavil, Ph.D., Sam Haider, Ph.D., Martin Yau, Ph.D.
OSE/DMEPA	Tara Turner, Pharm.D., Zachary Oleszczuk, Pharm.D., Denise Toyer, Pharm.D., Carol Holquist, R.Ph.
OSE/DRISK (patient labeling)	Steve Morin, R.N., B.S.N., O.C.N., Barbara Fuller, R.N., M.S.N., Sharon Mills, B.S.N., R.N., C.C.R.P.
OSE/DRISK (REMS)	Marcia Britt, Ph.D., Anges Plante, B.S.N., R.N., Megan Moncur, M.S., Claudia Karwoski, Pharm.D.
CSS	James Tolliver Ph.D., Silvia Calderon, Ph.D.
Biometrics (supporting CSS)	Ling Chen, Ph.D., Stella Machado, Ph.D.

1. Introduction

In accordance with 21 CFR 314 and Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Endo Pharmaceuticals Inc. has submitted an Original New Drug Application for oxymorphone hydrochloride [REDACTED] (b) (4) extended-release tablets as a 505(b)(1) application.

Endo Pharmaceuticals Inc. and its partner Grünenthal GmbH (Aachen, Germany) have developed an extended-release formulation of oxymorphone HCl that [REDACTED] (b) (4) is intended to reduce accidental misuse (i.e., breaking, and/or crushing for patient convenience) and to deter certain methods of intended abuse (i.e., crushing for snorting and/or injection).

The Applicant intends to base approval on establishing bioequivalence to OPANA ER (NDA 21-610), which was approved by the Agency on June 22, 2006, and is owned by Endo. The proposed product is intended to be dosed twice-daily and will be available in the same dosage strengths as OPANA ER (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg).

2. Background

Oxymorphone is a semisynthetic opioid analgesic, first approved in 1959 as Opana (oxymorphone 1mg/mL), a parenteral formulation indicated for the relief of moderate-to-severe pain, preoperative medication, support of anesthesia, obstetrical analgesia, and for relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular dysfunction. A second parenteral formulation, Numorphan, was approved in 1960. The first oral formulations were approved in June, 2006 and included immediate-release tablets, Opana, indicated for the relief of moderate-to-severe acute pain, and extended-release tablets, Opana ER, 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.

The abuse of prescription drugs, and in particular opioid analgesics, is a growing and devastating problem in the United States. Oxymorphone, a mu opioid agonist and a Schedule II controlled substance, is a known drug of abuse, and is sought by drug abusers and people with addiction disorders, and is subject to criminal diversion. One of the approaches to mitigate the abuse of prescription opioid drug products that has been recommended by the Agency, as well as by numerous other stakeholders, is the development of “abuse-resistant” formulations. FDA has encouraged the development of these formulations but has also been clear that we will not approve new indications for or labeling that is suggestive of abuse resistance for these new formulations unless an application is accompanied by data from long-term epidemiological studies that clearly demonstrate that abuse, misuse and diversion have been reduced. However, in order to provide some incentive to sponsors, above and beyond their public health responsibility, we have noted that we would consider allowing limited data from studies that evaluated the abuse-resistant features of the products to be added to appropriate sections of the labeling. This approach has been endorsed at several meetings of the Anesthetic and Life Support and the Drug Safety and Risk Management Advisory Committees, where other “abuse” and “tamper” resistant products have been discussed.

The review of this NDA has focused on the quality of the formulation, its bioequivalence to the already approved Opana ER, and the formulation’s [REDACTED] (b) (4) tamper-resistant qualities.

3. CMC/Device

The CMC review was completed by Craig Bertha Ph.D., with secondary concurrence from Prasad Peri, Ph.D. The following summarizes Dr. Bertha's review.

The drug product, oxymorphone extended-release tablets, is a solid dosage form with strengths 5, 7.5, 10, 15, 20, 30, and 40 mg (as the hydrochloride salt), intended for oral administration. The drug product is packaged in high-density polyethylene bottles that are fitted with child resistant closures, with each containing 60 or 100 tablets (for all strengths). The formulation for each strength consists of oxymorphone hydrochloride, in a [REDACTED] (b) (4) of polyethylene oxide, hypromellose, and polyethylene glycol. The formulation also contains [REDACTED] (b) (4) (b) (4) α-tocopherol (Vitamin E) [REDACTED] (b) (4) and citric acid [REDACTED] (b) (4) (b) (4) Manufacturing involves [REDACTED] (b) (4). All of the strengths have the same tablet weight (221.5 mg) and they are all film coated with different colorants (pink, gray, orange, white, green, red, yellow) to help distinguish the strength, along with the debossing of the numerical strength on one side of each tablet. [REDACTED] (b) (4)

The drug substance is oxymorphone hydrochloride, [REDACTED] (b) (4)

[REDACTED] (b) (4) no additional review of the CMC information related to production of that drug substance was needed to support this application.

The Office of Compliance issued an overall recommendation of Acceptable for this NDA on November 15, 2010.

The CMC review team has recommended approval for this application from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

A review was conducted by Elizabeth Bolan Ph.D., with secondary concurrence by Dan Mellon Ph.D. The following summarizes the review.

No nonclinical studies were conducted for this NDA. It was submitted under the 505(b)(1) regulatory pathway, and cross referenced the nonclinical pharmacology, ADME, and toxicology information provided in NDA 21-610 (Opana ER), and the rat and mouse carcinogenicity studies submitted to IND 56,919 (Oxymorphone ER), both owned by the Applicant.

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.

The Pharmacology/Toxicology team recommended some revisions to the proposed label that will be included in the approved label.

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology review was conducted by Srikanth Nallani, Ph.D., with secondary concurrence by Suresh Doddapaneni, Ph.D. The primary Biopharmaceutics review was conducted by Sandra Suarez Sharp, Ph.D., with secondary concurrence by Patrick Marroum, Ph.D. The following summarizes those reviews.

The Applicant submitted pharmacokinetic studies seeking approval of (b) (4) by demonstrating bioequivalence to their own OPANA ER product. Pharmacokinetics and tamper resistance properties of (b) (4) were evaluated under conditions of normal use and accidental misuse (i.e., breaking and/or crushing for patient convenience) and certain methods of intended abuse (i.e., crushing for snorting and/or injection, alcohol interaction and chewing).

Six pharmacokinetic studies were conducted in healthy volunteers to support the efficacy, safety (b) (4) of (b) (4) tablets as shown in the tables below from Dr. Nallani's review.

Table 1: Studies establishing bioequivalence of (b) (4) to Opana ER

Study # EN3288-103: BE study comparing (b) (4) 40 mg compared to OPANA ER 40 mg in healthy subjects under fasting state and naltrexone blockade.
Study # EN3288-104: BE study comparing (b) (4) 40 mg compared to OPANA ER 40 mg in healthy subjects under fed state and naltrexone blockade.
Study # EN3288-105: BE study comparing (b) (4) 5 mg compared to OPANA ER 5 mg in healthy subjects under fasting and naltrexone blockade.

Table 2: PK studies conducted to evaluate dose dumping of (b) (4) after improper use

Study # EN3288-107: Alcohol interaction study assessing relative bioavailability of (b) (4) 40 mg taken with or without an alcoholic beverage and naltrexone blockade.
Study # EN3288-108: Relative bioavailability study comparing (b) (4) 40 mg taken intact and after physical tampering (cutting, crushing and grinding) and naltrexone blockade.
Study # EN3288-109: Relative bioavailability and drug-liking study comparing (b) (4) 40 mg taken intact and after chewing <u>without naltrexone blockade</u> .

(b) (4) (oxymorphone ER)

Additional in vitro studies were performed by the Applicant to address if different methods of tampering with controlled-release products known to drug addicts would defeat the extended-release properties of [REDACTED] (b) (4). These studies were reviewed by Drs Sharp and Tolliver and will be discussed later in this review.

Bioequivalence of [REDACTED] (b) (4) to Opana ER was established with the highest dose, 40mg, and the lowest dose, 5mg, under fasting conditions. The adequacy of the in vitro dissolution profiles submitted in support of the biowaiver for the intermediate strengths was reviewed by Dr. Sharp and found acceptable. The table below from Sr. Nallani's review shows the results of the BE studies. Note that [REDACTED] (b) (4) 40mg is also bioequivalent to Opana ER 40mg under fed conditions.

Table 3: Summary Table of BE analyses of [REDACTED] (b) (4) compared to Opana ER

Parameter	Geometric Least Squares Means		Ratio of Means	90% Confidence Interval
	EN3288	OPANA ER		
EN3288-103: Single 40 mg Oral Doses to Fasted Healthy Subjects*				
Cmax (ng/mL)				(b) (4)
AUC0-t (ng•h/mL)				
EN3288-104: Single 40 mg Oral Doses to Healthy Subjects with a High-Fat Meal				
Cmax (ng/mL)	5.24	5.55	0.94	0.88-1.02
AUC0-t (ng•h/mL)	47.10	48.43	0.97	0.93-1.02
EN3288-105: Single 5 mg Oral Doses to Fasted Healthy Subjects				
Cmax (ng/mL)	0.352	0.360	0.98	0.93-1.03
AUC0-t (ng•h/mL)	5.04	4.82	1.05	1.01-1.09

Previously, during the review of OPANA ER in NDA 21-610, the Clinical Pharmacology reviewer noted a large food effect, such that the mean oxymorphone C_{max} in the fed state was about 52% higher than the C_{max} in fasted state. Since [REDACTED] (b) (4) and OPANA ER are bioequivalent under fasting and fed conditions, it can be assumed that [REDACTED] (b) (4) has the same degree of food effect as OPANA ER. Current dosing recommendations for OPANA ER indicate that the tablet should be dosed at least one hour prior to or two hours after eating. The same dosing recommendation will apply to [REDACTED] (b) (4).

Dr. Nallani discussed the extended-release profile of [REDACTED] (b) (4) under normal and improper use in his review. The Applicant conducted a study to evaluate alcohol drug interaction effects of consuming 20% or 40% alcohol on the pharmacokinetic profile of [REDACTED] (b) (4). The results indicated that similar to Opana ER, administration of beverages containing alcohol (20% and 40%) resulted in significant increase in peak plasma levels. On average, oxymorphone C_{max} increased with the amount of ethanol consumed and was 1.14-fold and 1.80-fold higher with 20% and 40% ethanol, respectively. Noteworthy is the fact that in certain individuals maximum fold change in C_{max} up to 2.5-fold or 5.5-fold were noted in 20% or 40% alcohol treatment groups compared to [REDACTED] (b) (4) alone.

(b) (4) (oxymorphone ER)

(b) (4) and OPANA ER are similar in their susceptibility to alcohol-related drug interaction. Interestingly, this interaction is not due to the failure of the extended-release characteristics of the formulation but is probably due to the alcohol effect on the absorption of oxymorphone itself. For both OPANA ER and (b) (4) in vitro dissolution studies have demonstrated that these products do not release oxymorphone more rapidly in dissolution media containing alcohol.

A study was conducted by the Applicant to evaluate dose dumping of oxymorphone under conditions of accidental or intentional misuse by breaking and/or crushing with different methods. It was an open-label, randomized, 6-sequence, 6-period crossover design with subjects randomized to the following treatments:

- A EN3288 40 mg – intact tablet
- B EN3288 40 mg – tablet tampered with a commercial pill crusher
- C EN3288 40 mg – tablet cut (b) (4)
- D EN3288 40 mg – tablet tampered (b) (4)
- E OPANA ER 40 mg – tablet tampered with a commercial pill crusher
- F OPANA 40 mg (4×10 mg) – intact tablets

The Applicant compared BE of (b) (4) following physical manipulation (B, C, and D) with Treatment A (intact ER tablets) or Treatment F (40mg IR tablets). Since the goal of this study is to understand whether the extended-release product can withstand physical tampering, PK results from an intact extended-release product is the more appropriate reference. Using intact (b) (4) as reference, peak plasma levels of oxymorphone failed bioequivalence and were significantly higher when (b) (4) was consumed following grinding and cutting indicating the loss of extended-release characteristics. However, the data indicates that (b) (4) resists physical crushing forces noted using a pill crusher (Treatment B) as demonstrated by bioequivalence to intact (b) (4) with respect to Cmax. In terms of individual data, fold increases in Cmax as high as 4-fold were noted with cutting or grinding the tablet. The following figure from Dr. Nallani's review illustrates the mean plasma oxymorphone profiles for the treatment groups.

Figure 1

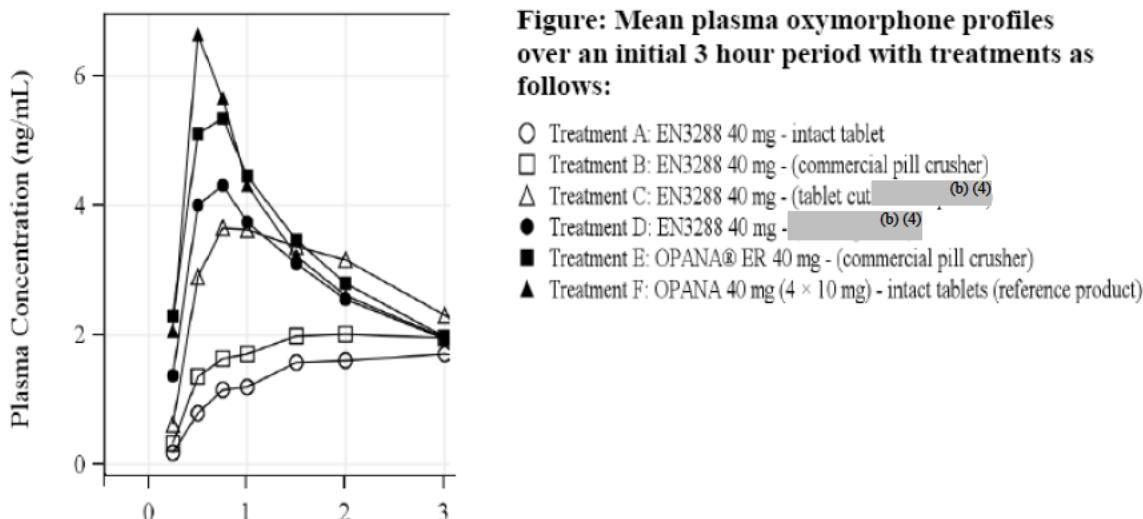


Figure: Mean plasma oxymorphone profiles over an initial 3 hour period with treatments as follows:

- Treatment A: EN3288 40 mg - intact tablet
- Treatment B: EN3288 40 mg - (commercial pill crusher)
- △ Treatment C: EN3288 40 mg - (tablet cut) (b) (4)
- Treatment D: EN3288 40 mg - (b) (4)
- Treatment E: OPANA® ER 40 mg - (commercial pill crusher)
- ▲ Treatment F: OPANA 40 mg (4 x 10 mg) - intact tablets (reference product)

The Applicant also conducted a study to evaluate the effect of mastication/chewing on the bioavailability of (b) (4) 40mg. No specific instructions were given to the study subjects regarding the rate or duration of chewing; they were instructed to completely and carefully chew the tablet for as long as possible. When compared to an intact (b) (4) tablet, there was a 2.2-fold increase in Cmax when (b) (4) is consumed after chewing. In terms of individual data, up to 6-fold increases in Cmax were noted when (b) (4) was consumed after chewing.

Below are conclusions of the Clinical Pharmacology review team as stated in Dr. Nallani's review.

Overall Conclusions:

1. (b) (4) 40 mg is bioequivalent to OPANA ER under fasted and fed conditions. At the time of writing this review, inspection report from DSI of study EN3288-103 is pending.
2. (b) (4) 5 mg is bioequivalent to OPANA ER under fasted condition.
3. Similar to OPANA ER, alcohol-related interaction results in high peak plasma levels.
4. Although (b) (4) seems to resist crushing by pill crusher, it is susceptible to defeat of extended-release characteristics by other methods of physical manipulation. Cutting and grinding (b) (4) resulted in a significant increase in peak plasma levels compared to intact product.
5. As demonstrated by significant increase in peak plasma levels compared to intact product, extended-release characteristics of (b) (4) were defeated when chewed and consumed.

The Biopharmaceutics team reviewed the dissolution methods and specification, the biowaiver request for intermediate doses based on the dissolution profile comparisons, and the in vitro alcohol interaction study.

Dr. Sharp noted in her review that the dissolution method and proposed specifications for all strengths of the (b) (4) tablets are acceptable. The dissolution profiles of all strengths in three different media were determined, and were similar. Therefore the waiver request of the in vivo BE requirements for the intermediate tablet strengths between 5mg and 40mg was granted.

When 40% ethanol was added to the dissolution media, dissolution rates of the 40mg tablets were slower, and there was no change in dissolution rates when 5% ethanol was added. These results are in contrast to the in vivo alcohol interaction study discussed earlier in this section.

Several in vitro studies were conducted to assess the tamper-resistant characteristics of (b) (4). The results of these studies are discussed in the review completed by the Controlled Substance Staff. However, Dr. Sharp notes in her review that (b) (4) does not show good resistance to tampering employed by recreational or experienced abusers, as evidenced by a 60% increase in the dissolution in one hour for tablets (b) (4) compared to intact tablets.

From the biopharmaceutics perspective, this NDA may be approved.

6. Clinical Microbiology

This section is not applicable to this NDA

7. Clinical/Statistical- Efficacy

No clinical efficacy studies were conducted in support of this application.

8. Safety

The Applicant submitted a Summary of Clinical Safety which included safety data from 240 subjects who received study drug in the pharmacokinetic and tampering studies. In six PK studies, subjects received naltrexone blockade, so the interpretation of the safety data in these studies is limited, as opioid associated adverse events would be blocked, and naltrexone could be the cause of the AEs. Results of the tampering studies will be discussed by the Controlled Substance Staff in their review.

Overall, adverse events reported with EN3288 were not different from those reported for OPANA ER. No deaths were reported during the development program, and there were no SAEs reported in subjects receiving any formulation of oxymorphone. The most frequently occurring events related to EN3288 were vomiting, nausea, dizziness, abdominal pain, and headache, all of which have been reported in the Opana ER label. No new safety signals were detected in the Applicant's studies.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

(b) (4) (oxymorphone ER)

10. Pediatrics

Pediatric studies are not required for this NDA, since as a new formulation of an approved drug, it does not trigger the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

Division of Scientific Investigation (DSI) Consult

DSI was consulted in order to inspect the study site that conducted Study EN288-103, An open-label, randomized, single dose, four-period, replicate, crossover study to determine the bioequivalence of EN3288 (Oxymorphone HCl extended-release [REDACTED] (b) (4) formulation) 40 mg compared to OPANA ER (Oxymorphone HCl extended-release) 40 mg in healthy subjects under fasted conditions.

The clinical portion of Study EN3288-103 was conducted at SeaView Research, Inc., Miami, FL. The analytical portion was conducted at [REDACTED] (b) (4)
was also the subject of a complaint received by the Agency in 2009 [REDACTED] (b) (4)

[REDACTED] This inspection served as a follow-up to an initial inspection that was conducted in response to the complaint. The site was issued a Form FDA 483 citing the infractions, and the Agency has not yet received a response. [REDACTED] (b) (4)

Details regarding the inspection report are found in the review completed by DSI. [REDACTED] (b) (4)

This is an approvability issue, since this study is one of two key studies establishing bioequivalence with Opana ER. If the firm responds acceptably to the DSI findings within the time period allotted by DSI, these inspection results may not preclude approval, however if not, this NDA will not be approved.

Controlled Substance Staff (CSS) Consult

CSS was consulted to review the in vitro manipulation and chemical extraction studies, a clinical pharmacokinetic study, human abuse potential studies, and two bench top

(b) (4) (oxymorphone ER)

attractiveness studies. For details, refer to the CSS review. The conclusions and recommendations of the Controlled Substance Staff are as follows:

- (b) (4) provides limited resistance to physical and chemical manipulation for abuse. (b) (4) extended-release mechanism can be overcome by cutting, chewing or grinding. Intake of (b) (4) with food or alcohol increases blood levels of oxymorphone. (b) (4) tablets provide some resistance to crushing using simple tools (b) (4) (b) (4)
- The Sponsor did not conduct studies to demonstrate that (b) (4) tablets can be abused intranasally. However, the difficulty in crushing (b) (4) tablets (b) (4) as observed in the in vitro studies makes it less likely that, relative to Opana ER, individuals will intranasally abuse (b) (4) manipulated using these tools. The bench top study demonstrated the difficulty in forming an intranasal preparation (b) (4). However the in vitro studies and the bench top study did not address the grinding of (b) (4) tablets for possible abuse by intranasal administration.
- (b) (4) tablets are more difficult to cut than OPANA ER tablets. (b) (4) tablets can be cut (b) (4) compromising the extended-release properties of the formulation
- An in vitro study conducted by the Sponsor showed that it might be easier to prepare a solution for injection when using (b) (4) than when using OPANA ER. Exposure of a crushed Revopan 40mg tablet (b) (4) of the label claim of extracted oxymorphone HCl. However, the bench top manipulation study, Study EN 3288-901, showed that both formulations behaved similarly.
- Grinding the (b) (4) tablets severely compromises the controlled release of oxymorphone HCl, as demonstrated by the high percentages of label claim of oxymorphone HCl (b) (4). These percentages of label claim (b) (4) represent extraction levels ranging from (b) (4) of oxymorphone. Considering that at equianalgesic doses, oral oxymorphone is (b) (4) more potent than oral oxycodone when physiological opioid effects (miosis, hypotension, analgesia) are compared, the extracted amounts of oxymorphone are equivalent in its opioid effects of analgesia, miosis, and respiratory depression to (b) (4) of oral oxycodone respectively.
- (b) (4) manipulated (b) (4) tablets or OPANA ER tablets might be difficult,
- Clinical abuse liability study EN3288-109 demonstrates that mastication of (b) (4) 40 mg tablets compromises the controlled-release mechanism of (b) (4)
- Based on the results of pharmacokinetic study EN3288-108 and abuse liability study EN3288-109, it is likely that the ingestion of a (b) (4) 40 mg tablet cut (b) (4) will produce substantial and statistically significant subjective reinforcing effects above those produced by the ingestion of intact (b) (4) 40 mg tablets. In addition food increases the absorption of oxymorphone, thus increasing the likeability of oxymorphone containing products including (b) (4)

CSS Recommendations:

- That the product label not include language asserting that [REDACTED] (b) (4) provides resistance to crushing.
- Conduct a study to determine if [REDACTED] (b) (4) could be administered intranasally, if such a study can be conducted safely. This study is relevant considering that the most prominent route of abuse of OPANA ER is intranasal, followed by the oral and intravenous routes as reported by adult individuals ages 18 years and older entering treatment (Addiction Severity Index-Multimedia Version (ASI-MV) 2009- Data presented at FDA Joint Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee held October 21-22, 2010 in Gaithersburg, Maryland).

In regards to the recommendation for the Applicant to perform an intranasal study, there is currently inadequate preclinical data to support such a study with the [REDACTED] (b) (4) formulation. Also, the presence of the excipient polyethylene oxide (PEO) in [REDACTED] (b) (4) may cause the product to get stuck in the nose and result in additional safety concerns. The overall safety concerns associated with PEO are discussed below. The Division has requested that CSS provide information they may have regarding safe conduct of a study of intranasal [REDACTED] (b) (4) and also convey the request for the study to the Applicant in a Discipline Review letter, stating that a study of intranasal [REDACTED] (b) (4) may be useful if it can be conducted in a safe manner and with adequate preclinical support. Although such a study could yield useful information regarding the intranasal route of abuse of [REDACTED] (b) (4) there will not be a postmarketing requirement that the study be conducted, due to safety concerns at this time.

Safety Concerns Regarding the [REDACTED] (b) (4) Formulation

Polyethylene oxide (PEO) is an excipient in [REDACTED]

(b) (4)

[REDACTED] and has been an excipient in a number of approved drugs. For a recently approved drug, a reformulation of Oxycontin (NDA 22-272) that contains PEO, there have been a number postmarketing reports of choking and sticking in the GI tract, including some serious cases. This is likely due to the presence of PEO that causes the tablets to become sticky when wet. There are also drug products that contain PEO where choking and sticking adverse events have not been reported.

There have been no reports of sticking or choking during the [REDACTED] (b) (4) development program, however the only Phase 1 studies were conducted, where subjects were instructed to consume the tablet with eight ounces of water. Therefore the absence of cases does not guarantee that choking or sticking with [REDACTED] (b) (4) would not occur in situations where the patient does not take the tablet with adequate water or wets the tablet prior to ingestion.

Consequently, the labeling for [REDACTED] (b) (4) will include instructions for the patient to take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. The Applicant must also conduct a postmarketing requirement that consisting of heightened pharmacovigilance for adverse events related to the formulation such as choking or sticking in the GI tract.

Risk Evaluation and Mitigation Strategies

As an extended-release Schedule II opioid, a REMS is required for the approval of this product to inform patients and providers about the potential for misuse, abuse, overdose, and addiction. The current REMS requirements for drugs in the class are a Medication Guide, an element to assure safe use (prescriber training), and a Timetable for REMS assessments. (b) (4) will become part of the class-wide long-acting opioid REMS when it ultimately takes effect.

The Applicant submitted a proposed REMS and REMS Supporting Document a Dear Healthcare Professional Letter, a Dear Pharmacist Letter, and a Healthcare Professional Training Guide, a Package Insert and a Medication Guide. This is being reviewed by OSE/DRISK, and comments were sent to the Applicant on December 10, 2010.

The REMS review is ongoing at this time. A finalized REMS must be part of the approval for (b) (4)

12. Labeling

The Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proprietary name (b) (4) and found it acceptable for this product.

DMEPA has also reviewed the carton and container and provided comments for the Applicant.

The Medication Guide was reviewed by the DRISK patient labeling team who provided comments. Their comments will be sent to the Applicant.

The Division of Drug Marketing, Advertising, and Communications has reviewed the label and provided revisions.

Due to the marked food effect associated with (b) (4) the label will state that (b) (4) must be taken on an empty stomach, at least one hour prior to or two hours after eating.

CSS has recommended that the label not include language asserting that (b) (4) provides (b) (4) resistance to crushing (b) (4) The (b) (4)

Division agrees with this,

since the extended-release characteristics of the formulation are compromised by cutting, chewing or grinding.

The label will also include instructions for the patient to take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth, due to concerns regarding the potential choking and sticking resulting from the PEO in the formulation.

Labeling negotiations between the Agency and the Division are ongoing at this time.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response due to deficiencies in the methods used at the analytical site for a key bioequivalence study, EN3288-103, as determined by the Division of Scientific Investigations.

- Risk Benefit Assessment

The Applicant developed an extended-release formulation of oxymorphone HCl [REDACTED] (b) (4) intended to reduce accidental misuse and to deter certain methods of intended abuse. They planned to base the approval on establishing bioequivalence to Opana ER. The proposed product is intended to be dosed twice-daily and will be available in the same dosage strengths as OPANA ER (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg), and have the same indication.

[REDACTED] (b) (4) was shown to be bioequivalent to Opana ER in two Phase 1 studies that demonstrated bioequivalence of the 5mg and 40mg doses. A biowaiver was granted for the intermediate doses based on dissolution profile comparisons.

Safety data was obtained from the pharmacokinetic studies, however since most of the subjects received naltrexone blockade, the data is of minimal use. However, no new safety signals compared to those labeled for Opana ER were detected. As the Applicant relied on the Agency's previous findings of safety and efficacy for Opana ER, and [REDACTED] (b) (4) was shown to be bioequivalent to Opana ER, no additional safety or efficacy studies were required.

Reviews of the [REDACTED] (b) (4) abuse liability characteristics of [REDACTED] (b) (4) by the clinical pharmacology team and the Controlled Substance Staff showed that although [REDACTED] (b) (4) appears resistant [REDACTED] (b) (4) the extended-release characteristics of the formulation are compromised by chewing, cutting and grinding. [REDACTED] (b) (4)

(b) (4)

There is a potential safety concern regarding the polyethylene oxide (PEO) in the formulation. Postmarketing adverse events that include choking and sticking have been observed with another extended-release opioid that contains PEO. These events were not observed during the development of [REDACTED] (b) (4) however the tablets were taken under controlled conditions. The Division has determined that if the label includes patient instructions to take the tablets one at a time with sufficient water, and a postmarketing requirement of enhanced pharmacovigilance is put in place, this safety issue will not preclude approval.

There is one outstanding issue that precludes approval of this NDA. The DSI inspection of the analytical site for Study EN3288-103, [REDACTED] (b) (4) showed deficiencies in the analysis of the samples such that the results of Study EN3288-103 should not be accepted in support of this NDA. The firm was given a time frame of two weeks in which to respond to the deficiencies, of which one week remains.

- Recommendation for Postmarketing Risk Management Activities

As an extended-release opioid, a REMS is required for approval. The REMS must include a Medication Guide, an element to assure safe use (prescriber training), and a Timetable for Assessments. The Applicant has submitted a proposed REMS including the required elements, which is currently under review by DRISK. Agreement on the REMS must be reached prior to approval.

- Recommendation for other Postmarketing Study Commitments

Because there have been reports of choking and tablets sticking in the gastrointestinal tract in patients taking a different opioid product that contains polyethylene oxide (PEO), the Applicant is required to conduct enhanced postmarketing pharmacovigilance for adverse events possibly related to the formulation, such as choking, sticking, and GI obstruction, and to determine the characteristics of patients who are at risk for development of these reactions.

This should include an assessment and analysis of spontaneous reports of gastrointestinal adverse events including choking, sticking, and obstruction associated with [REDACTED] (b) (4). Following approval, and according to a specified timetable, the Applicant must submit the reports (containing both interval-based and comprehensive data) analyzing spontaneous adverse event reports received that describe serious reactions. Specialized follow-up should be obtained on these cases to collect additional information on the event. The summaries of reported cases of choking, sticking or obstruction should include an analysis of patient factors, provider factors and administration factors, or any other information that may lead to improved safe use of [REDACTED] (b) (4). The Applicant will be informed of this requirement and asked to submit their proposal for the pharmacovigilance program.

- Recommended Comments to Applicant

1. An audit performed by the Agency of the bioequivalence study EN3288-103 to establish bioequivalence of the active ingredient oxymorphone to the reference product identified deficiencies in the methods used at the analytical sites. Because of these deficiencies, the bioequivalence study cannot be relied upon to establish bioequivalence of your proposed drug product to the reference products.

This deficiency may be addressed by doing the following:

- a) Conduct another single-dose clinical pharmacology study to establish the bioequivalence of your proposed oxymorphone extended-release tablet, [REDACTED] (b) (4) to the reference product, Opana ER.

OR

- b) Conduct a clinical development program with clinical efficacy and safety studies to support your product

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/s/

ELLEN W FIELDS
12/22/2010
NDA 201655 CDTL Memo
Recommended Complete Response

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201658 Applicant: Euro

Stamp Date:

Drug Name: ~~oxymorphone~~ (b) (4) NDA/BLA Type:
oxymorphone ER

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			✓	electro
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	✓			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	✓			
5.	Are all documents submitted in English or are English translations provided when necessary?	✓			
6.	Is the clinical section legible so that substantive review can begin?	✓			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	✓			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		✓		OK per PNDA months
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓		✓	
11.	Has the applicant submitted a benefit-risk analysis for the product?	✓			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	✓			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Location in submission:			✓	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			✓	

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			✓	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			✓	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			✓	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✓			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			✓	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		✓		no Pm Optm BN ICH submitted & request
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			✓	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			✓	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?				
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✓			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	✓			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			✓	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			✓	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		✓		<i>Waived per PDUFA moniker</i>
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	✓			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			✓	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			✓	
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			✓	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			✓	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	✓			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Nori

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

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/s/

ROBERT B SHIBUYA
08/23/2010