CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-610

21-611

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

2nd Cycle

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-610 21-611	Submission Date: 12/22/05
Submission Type; Code:	**Response to Approvable Action Letter Dated 12/25/05**
Brand/Code Name:	To-be-determined
Generic Name:	Oxymorphone Hydrochloride
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
ORM Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Sponsor:	Endo Pharmaceuticals Inc.
Relevant IND(s):	58,602; 56,919
Relevant NDA(s):	11-707; 11-738
Formulation; Strength(s):	5, 10 mg IR 5, 10, 20, 40 mg ER
Proposed Indication:	Management of moderate to severe pain where the use of an opioid is appropriate
Proposed Dosage Regimen:	This is contraindicated in patients with severe hepatic impairment. The dose should be titrated (initiate with IR every 6 — as needed and maintain pain management with ER bid) based upon the individual patient's response and condition (e.g., opioid-naïve patients should be started on 5 mg IR every 6 ⌣ as needed.)

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1 Executive Summary

Endo Pharmaceuticals Inc. has originally submitted NDA 21-610 (ER tablet) and 21-611 (IR tablet) for the Oxymorphone IR and ER formulations on 12/19/02. On 10/15/03, the Applicant was sent an approvable action (AE) letter along with Agency's preliminary labeling comments. In the current submission, the Applicant has submitted the Complete Response, which includes the responses to all the deficiencies and the labeling comments.

With respect to Clinical Pharmacology, there were no identified deficiencies in the AE letter. However, the Applicant has submitted the following new information : 1) in vitro/in vivo alcohol-oxymorphone ER interaction results, 2) food effect study results (two studies), 3) IR single- and multiple-dose information, and 4) results from a simulation of 4-and 8-hr IR multiple dosing regimens, based on a single-dose IR 6-hr pharmacokinetic information. The Applicant additionally submitted pediatric plan (outline) to study both IR and ER formulations in 2-16 years old for acute and chronic pain (in opioid tolerant patients).

In vitro alcohol-oxymorphone ER formulation dissolution results show that there is no potential for ER formulation to 'dose-dump' in the presence of alcohol. The tablets were intact throughout the dissolution test. The release rate correlates inversely with the amount of ethanol, that is, with higher alcohol amount, the dissolution rate was retarded.

However, the in vivo alcohol interaction study showed that both 20% and 40% alcohol treatments 'dose-dumped' the oxymorphone. The geometric mean ratios showed that Cmax was 70% (ratio range 1.1 – 3.7), 31% (ratio range 0.6 – 3.6), and 7% higher for the 40%, 20% and 4% ethanol treatments, respectively, compared to the 0% ethanol treatment. Statistically significant differences were observed for 40 and 20% alcohol groups. Effect on AUC was not significant. The geometric mean ratio showed that AUC was 13% higher (not statistically significant) for the 40% alcohol treatment group

compared to the 0% alcohol treatment group. Other alcohol groups' AUCs were similar to that of 0% group. Currently, the conflicting results between in vitro and in vivo data can not be explained based on available data.

It is noted that food effect information was previously submitted in the original NDA. The food effect information submitted in the Response is similar to the previously submitted information (IR formulation – Cmax and AUC increased by approx. 38%; ER formulation – Cmax increased approx. 50-58%, AUC did not change).

Oxymorphone IR 5, 10 and 20 mg exhibited dose linearity after single- and multiple dosing (q6h for 4 days). Using q6h data, 4- and 8-hour dosing regimen was simulated. Comparing the q6h simulated and actual pharmacokinetic parameters, the simulation underestimated the average steady-state plasma concentrations by 14 – 25 %. It is expected that similar results may be obtained for q4h and q8h dosing regimen.

Overall, there are no issues with the Complete Response. However, there are Labeling comments (Section 3 Detailed Labeling Recommendations). Regarding pediatrics, Sponsor may submit a PPSR in the near future and pediatric pharmacokinetic data requirements will be worked out at that time when a comprehensive proposal is made by the sponsor. .

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology Evaluation II (OCP/DCP-II) has reviewed the Complete Response submitted on 12/22/05.

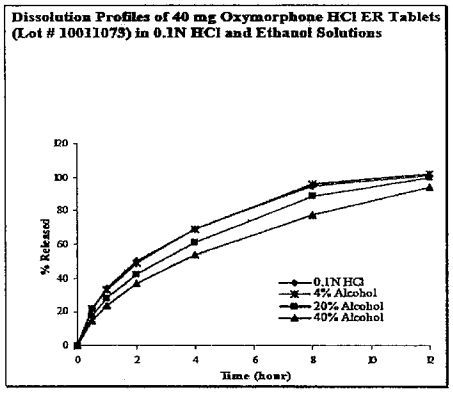
From the OCP perspective, the information contained in the Response is acceptable provided that a mutually satisfactory agreement is reached between the Applicant and the Agency on Labeling (Section 3 Detailed Labeling Recommendations).

1.2 Phase IV Commitments – Not Applicable

1.3 Summary of CPB Findings

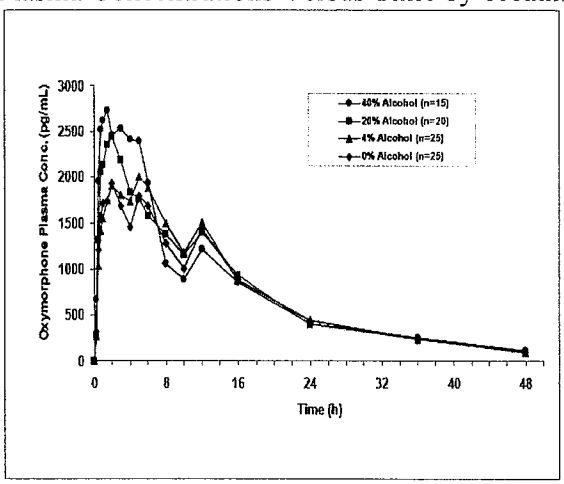
Alcohol-oxymorphone formulation interaction

In vitro dissolution profiles of 40 mg oxymorphone hydrochloride ER tablets were compared in 0.1 N HCl and ethanol/0.1 N HCl solutions at 4%, 20% and 40% ethanol concentrations. The results of this study on the extended-release formulation did not indicate a potential for product dose dumping in the presence of alcohol. The tablets were intact throughout the dissolution tests in all media. The release rate correlates inversely with the amount of ethanol, that is, with higher alcohol amount, the dissolution rate was retarded. The similarity factors relative to the 0.1N HCl medium are [redacted] – for the 4%, 20% and 40% ethanol solutions, respectively. The dissolution profile is presented in figure below.



In vivo alcohol-oxymorphone ER tablet interaction study was conducted. This was an open-label, randomized, single-dose, four-period crossover design. Twenty-eight subjects were randomly allocated to receive a single dose of EN3202 40 mg ER co-administered with 240 mL of either an ethanol solution or water over four periods, with each period separated by a minimum 7-day washout period. All subjects received treatment under fasted conditions. Frequently occurring TEAEs included vomiting, headache, nausea and dizziness.

Mean Oxymorphone Plasma Concentrations Versus Time by Treatment):

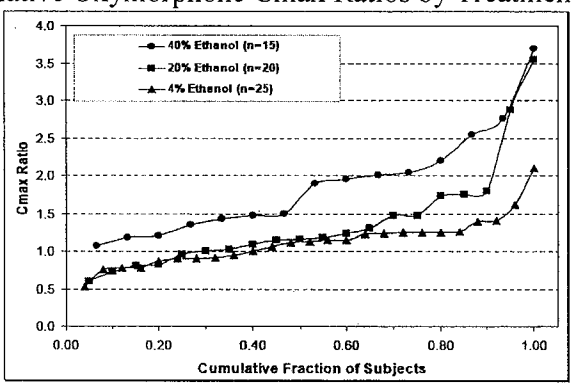


The geometric mean ratios showed that Cmax was 70% (ratio range 1.1 – 3.7), 31% (ratio range 0.6 – 3.6), and 7% higher for the 40%, 20% and 4% ethanol treatments, respectively, compared to the 0% ethanol treatment. Statistically significant differences were observed for 40 and 20% alcohol groups. For AUC, alcohol effect was not significant. The geometric mean ratio showed that AUC was 13% higher (not statistically significant) for the 40% alcohol treatment group compared to the 0% alcohol treatment group. Other alcohol groups' AUCs were similar to that of 0% group.

Individual subject Cmax ratios are plotted below. These ratios are shown as the cumulative fraction of subjects within a treatment. For example, for the 40% ethanol treatment, one-half of the subjects had a Cmax ratio below 1.5; 0.8 (80%) of the subjects

had a Cmax ratio below 2.2. The Cmax ratio for the 40% ethanol treatment was consistently higher than the other two ethanol treatments. The 20% ethanol treatment did not diverge from the 4% ethanol treatment until a cumulative fraction of approximately 0.65, and a large divergence was only seen for the last two subject values (cumulative fraction above 0.92).

Cumulative Oxymorphone Cmax Ratios by Treatments:



Currently, the divergence between in vitro and in vivo results can not be explained from the available information. In search of possible explanations, chemical and physiological aspects are considered.

According to the Merck Index, oxymorphone is freely soluble in water (1g in 4 ml). It may not be soluble in alcohol, but, solubility may not be a problem once it is with in the GI tract. It is known that alcohol induces CYP450 2E1 enzymes. However, oxymorphone does not undergo 2E1 metabolism. Further, collective evidence suggested that the cytochrome P450 enzymes do not appear to play a significant role in the phase I metabolism of oxymorphone. Alcohol has not been reported to affect the glucuronidation pathway and as such the alcohol's effect on metabolic pathway of oxymorphone seems unlikely. It is also known that alcohol induces absorption by increase in permeability (e.g., disruption of the membrane, etc.) in the gastrointestinal tract. It's Octanol /Aqueous partion coefficient (Log P) is 0.98 and permeability data qualifying oxymorphone as a high or low permeability drugis not available. In vitro dissolution data indicated that alcohol did not alter the release of oxymorphone from the ER formulation, indicating that 40% alcohol did not contribute to the oxymorphone exposure. It is conceivable that alcohol may disrupt the GI membrane such that the 'rate of absorption' is enhanced. If this is the case, the Tmax may have decreased as well. However, looking at the with-in subject Tmax value along with the Cmax information from the in vivo study, there is no trend or correlation between higher Cmax and shorter Tmax. Therefore, currently, the divergence between in vitro and in vivo results can not be explained.

Food effect

It is noted that food effect information was previously submitted in the original NDA (for IR - food increased both oxymorphone Cmax and AUC by 38%; for ER - food increased oxymorphone Cmax by 50%, which the AUC was unchanged in one study and increased by 18% in the other study). The food effect information submitted in the Response is similar to the previously submitted information.

Study EN3202-003: This study was a Phase I, randomized, single-dose, fed-fasted, four-way crossover bioavailability study using Oxymorphone ER (20 mg) tablet and Oxymorphone Oral solution (10 mg). Subjects were either fasted overnight or given a standardized high-fat meal. All treatments were taken with 240 mL of water.

For 20 mg ER tablet, with food, oxymorphone Cmax and AUC values increased 58% and 18%, respectively. For 10 mg oxymorphone solution, with food, Cmax and AUC values increased 50% and 32%, respectively.

For 20 mg ER tablet, with food, 6-OH-oxymorphone Cmax and AUC values decreased and increased 9% and 9%, respectively. For 10 mg oxymorphone solution, with food, 6-OH-oxymorphone Cmax and AUC values decreased and increased 35% and 6%, respectively.

Study EN3202-008: This study was a Phase I, randomized, single-dose, fed-fasted, four-way crossover bioavailability study using Oxymorphone ER (40 mg) tablet and Oxymorphone IR (4x10mg). Subjects were either fasted overnight or given a standardized high-fat meal. All treatments were taken with 240 mL of water.

For 40 mg ER tablet, with food, oxymorphone Cmax value increased 51%, however, oxymorphone AUC did not change with food. For 40 mg ER tablet, with food, 6-OH-oxymorphone Cmax value decreased 14%, however, 6-OH-oxymorphone AUC did not change with food.

For 4x10 mg IR tablet, with food, both oxymorphone Cmax and AUC values increased 38%. For 4x10 mg IR tablet, with food, 6-OH-oxymorphone Cmax value decreased 37%, however, 6-OH-oxymorphone AUC did not change with food.

IR single- and multiple-dose pharmacokinetics

A randomized three-period crossover study was conducted with single- and multiple-dosing design, with 5, 10, or 20 mg oxymorphone IR. On Day 1, subjects received a single dose. On Day 3 through the morning of Day 8, subjects received the same dose every 6 hours. Trough concentrations were measured prior to administration of the morning dose on Days 6, 7, and 8. Examination of the trough concentrations indicates that steady-state conditions were achieved by Day 6 or Day 7 for all three analytes. The treatments were separated by a 7-day washout period. Subjects received 50 mg dose of naltrexone once daily beginning on the evening prior to the first day and continued until

the evening of Day 7. See below tables for single- and multiple-dose pharmacokinetic parameters.

Single dose oxymorphone parameters:

Variable	EN3203 (5 mg)	EN3203 (10 mg)	EN3203 (20 mg)
AUC (ng•hr/mL)	**4.48 (2.07)**	**9.10 (3.40)**	**20.07 (5.80)**
AUCT (ng•hr/mL)	2.77 (1.40)	6.76 (3.18)	17.67 (5.76)
AUC0-6 (ng•hr/mL)	2.11 (1.00)	4.28 (1.49)	9.29 (3.04)
Cmax (ng/mL)	**1.10 (0.55)**	**1.93 (0.75)**	**4.39 (1.72)**
Tmax (hr)[a]	0.50 (0.25-1.00)	0.50 (0.25-1.50)	0.50 (0.25-1.00)
CL/F (L/min)	23.53 (13.18)	21.42 (9.92)	18.21 (6.16)
λz (hr-1)	0.1534 (0.1308)	0.1257 (0.0997)	0.0835 (0.0331)
t½ (hr)	**7.25 (4.40)**	**7.78 (3.58)**	**9.43 (3.36)**

Multiple dose oxymorphone parameters:

Variable	5 mg q 6 hr	10 mg q 6 hr	20 mg q 6 hr
AUCss (ng•hr/mL)	**4.63 (1.49)**	**10.19 (3.34)**	**21.10 (7.59)**
Cmax (ng/mL)	**1.73 (0.62)**	**3.51 (0.91)**	**7.33 (2.93)**
Cmin (ng/mL)	0.49 (0.17)	1.16 (0.43)	2.47 (0.94)
Tmax (hr)[a]	0.50 (0.25-6.00)	0.50 (0.25-1.00)	0.50 (0.25-1.50)
Cavg (ng/mL)	0.77 (0.25)	1.70 (0.56)	3.52 (1.27)
CL/F (L/min)	19.23 (4.27)	17.63 (4.42)	17.68 (6.14)
FI	1.62 (0.45)	1.46 (0.49)	1.39 (0.42)
R	2.41 (0.73)	2.54 (0.83)	2.34 (0.71)

AUCss : Area under the concentration versus time curve from time 0 to the end of one dosage interval at steady-state (i.e., time 0 to τ); calculated using linear trapezoid rule.

R (Accumulation Ratio) : calculated as AUC_{ss}/AUC_{0-6} or $C_{min(ss)}/C_{min(1)}$.

The dose-normalized AUC values for both oxymorphone and 6-OH-oxymorphone after the 5 and 10 mg doses are lower than those observed following the 20 mg dose, although not statistically different. The oxymorphone oral clearance (CL/F) values following the 5 and 10 mg doses reflect the observed AUC differences.

Analysis of dose proportionality for single dose (dose normalized to 10 mg):

PK Variable	5 mg	10 mg	20 mg	p-value
OXM				
ln-AUC (ng•hr/mL)	8.09 (1.05)	8.49 (1.05)	9.65 (1.05)	0.0627
ln-Cmax (ng/mL)	2.00 (1.06)	1.80 (1.06)	2.04 (1.06)	0.2124
ln-CL/F (L/min)	20.61 (1.05)	19.62 (1.05)	17.27 (1.05)	0.0627
6-OH-OXM				
ln-AUC (ng•hr/mL)	6.17 (1.08)	8.54 (1.08)	11.04 (1.08)	0.0000
ln-Cmax (ng/mL)	1.67 (1.06)	1.46 (1.06)	1.64 (1.06)	0.1888
OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone				

Steady-state proportionality was assessed following normalization of the pharmacokinetic variables to a 10 mg dose rather than the protocol-specified 5 mg. Log-transformed results were then compared across treatment groups.

Analysis of dose proportionality at steady-state (dose normalized to 10 mg):

Parameter	5 mg q 6 hr	10 mg q 6 hr	20 mg q 6 hr	p-value
OXM				
ln-AUCss (ng•hr/mL)	8.91 (1.03)	9.76 (1.03)	9.97 (1.03)	0.0600
ln-Cmax (ng/mL)	3.31 (1.05)	3.41 (1.05)	3.44 (1.05)	0.8338
ln-CL/F (L/min)	18.70 (1.03)	17.08 (1.03)	16.72 (1.03)	0.0600
6-OH-OXM				
ln-AUCss (ng•hr/mL)	9.14 (1.04)	9.99 (1.04)	10.83 (1.04)	0.0169
ln-Cmax (ng/mL)	2.91 (1.04)	2.94 (1.04)	3.19 (1.04)	0.1935
OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone; OXM-3-G=oxymorphone-3-glucuronide				

Following dose-normalization, there were no statistically significant differences across the three treatment groups for oxymorphone, AUCss, Cmax, or CL/F. This analysis confirms that the pharmacokinetics of oxymorphone are both linear and dose proportional at steady-state. Similar findings were observed for the metabolites.

4- and 8-hour dosing regimen simulation

Using the information obtained from Study EN3203-006, the Applicant conducted a simulation study to examine the 4- and 8-hour dosing regimen. Administration of oxymorphone immediate-release tablets has been recommended at 4 to 6- hourly intervals; and during as needed use, 20 mg doses were observed to be used on an 8-hourly dosage interval. The steady-state pharmacokinetics of oxymorphone have been studied when administered in a 6-hourly regimen, but not during 4- or 8-hourly administration. Steady-state concentrations were simulated from single-dose concentrations using the superposition method. Concentrations between existing time points were estimated by linear interpolation. It should be noted that modeling information (e.g., control files, data files, etc.) was not included in the Submission. The information from this modeling exercise should be considered as nice to know information at this time.

The Cmax ratios of predicted/observed were **0.75, 0.77, and 0.86** for the 5, 10, and 20 mg doses, respectively. That is, based on Cmax, the simulated (predicted by superposition) average steady-state plasma concentrations underestimated 25, 23, and 14% for 5, 10, and 20 mg doses, respectively, compared to that of the observed values from Study EN3202-006. Again, due to the fact that some of the blood concentrations in the 5 and 10 mg treatment groups were near the limit of detection in Study EN3203-006, 5 and 10 mg data should be taken with caution. It is expected that similar results may be obtained from 4- and 8-hour dosing regimens.

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2 QBR

2.1 General Attributes of the Drug

2.1.1 What are the proposed mechanism of action and therapeutic indication(s)?

Oxymorphone tablet is indicated for the management of moderate to severe pain where the use of an opioid is appropriate. Oxymorphone is an opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, fentanyl, codeine, and hydrocodone. In addition to analgesia, other pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression. Like all full opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic affect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS (central nervous system) opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. In addition, opioid receptors have been identified within the PNS (peripheral nervous system). The role that these receptors play in these drugs' analgesic effects is unknown.

2.2 General Clinical Pharmacology

2.2.1 Exposure-response

2.2.1.1 What are the single dose and multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section)

Study EN3203-006

A randomized three-period crossover study was conducted with single- and multiple-dosing design, with 5, 10, or 20 mg oxymorphone IR. On Day 1, subjects received a single dose. On Day 3 through the morning of Day 8, subjects received the same dose every 6 hours. Trough concentrations were measured prior to administration of the morning dose on Days 6, 7, and 8. Examination of the trough concentrations indicates that steady-state conditions were achieved by Day 6 or Day 7 for all three analytes. The treatments were separated by a 7-day washout period. Subjects received 50 mg dose of naltrexone once daily beginning on the evening prior to the first day and continued until the evening of Day 7.

Single dose:

Mean (SD) single-dose pharmacokinetic parameters:

Variable	EN3203 (5 mg)	EN3203 (10 mg)	EN3203 (20 mg)
OXM			
AUC (ng•hr/mL)	**4.48 (2.07)**	**9.10 (3.40)**	**20.07 (5.80)**
AUCT (ng•hr/mL)	2.77 (1.40)	6.76 (3.18)	17.67 (5.76)
AUC0-6 (ng•hr/mL)	2.11 (1.00)	4.28 (1.49)	9.29 (3.04)
Cmax (ng/mL)	**1.10 (0.55)**	**1.93 (0.75)**	**4.39 (1.72)**
Tmax (hr)[a]	0.50 (0.25-1.00)	0.50 (0.25-1.50)	0.50 (0.25-1.00)
CL/F (L/min)	23.53 (13.18)	21.42 (9.92)	18.21 (6.16)
t½ (hr)	7.25 (4.40)	7.78 (3.58)	9.43 (3.36)
6-OH-OXM			
AUC (ng•hr/mL)	4.02 (3.18)	9.90 (5.13)	24.37 (10.50)
AUCT (ng•hr/mL)	2.63 (2.37)	6.84 (4.15)	18.68 (8.54)
AUC0-12 (ng•hr/mL)	1.73 (0.97)	3.31 (1.51)	7.11 (2.71)
Cmax (ng/mL)	0.95 (0.52)	1.62 (0.75)	3.57 (1.41)
Tmax (hr)[a]	0.50 (0.25-1.00)	0.50 (0.50-1.50)	0.50 (0.25-1.00)
t½ (hr)	7.27 (4.76)	13.72 (6.55)	18.35 (5.77)
OXM-3-G			
AUC (ng•hr/mL)	650.03 (140.05)	1322.72 (261.76)	2672.40 (480.33)
AUCT (ng•hr/mL)	542.59 (144.80)	1210.92 (263.10)	2532.77 (511.59)
AUC0-12 (ng•hr/mL)	342.81 (72.48)	696.26 (154.65)	1375.09 (313.51)
Cmax (ng/mL)	134.24 (30.02)	265.78 (63.24)	516.26 (106.53)
Tmax (hr)[a]	1.00 (1.00-1.50)	1.00 (1.00-2.00)	1.00 (1.00-1.50)
t½ (hr)	8.48 (3.11)	9.15 (2.18)	9.67 (2.71)
a: median (range)			
OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone; OXM-3-G=oxymorphone-3-glucuronide			

For 5 and 10 mg dosing group, plasma concentrations were close to the detection limit. As such, there were large differences between the oxymorphone AUCT and AUC values. Single-dose proportionality was assessed by normalizing to 10 mg dose.

Analysis of dose proportionality for single-dose administration normalized to 10 mg:

PK Variable	5 mg	10 mg	20 mg	p-value
OXM				
ln-AUC (ng•hr/mL)	8.09 (1.05)	8.49 (1.05)	9.65 (1.05)	0.0627
ln-Cmax (ng/mL)	2.00 (1.06)	1.80 (1.06)	2.04 (1.06)	0.2124
ln-CL/F (L/min)	20.61 (1.05)	19.62 (1.05)	17.27 (1.05)	0.0627
6-OH-OXM				
ln-AUC (ng•hr/mL)	6.17 (1.08)	8.54 (1.08)	11.04 (1.08)	0.0000
ln-Cmax (ng/mL)	1.67 (1.06)	1.46 (1.06)	1.64 (1.06)	0.1888
OXM-3-G				
ln-AUC (ng•hr/mL)	1276.0 (1.02)	1305.2 (1.02)	1322.1 (1.02)	0.3168
ln-Cmax (ng/mL)	262.2 (1.02)	258.6 (1.02)	254.1 (1.02)	0.4695
Source: Appendix 2.19				
OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone; OXM-3-G=oxymorphone-3-glucuronide				

The dose-normalized AUC values for both oxymorphone and 6-OH-oxymorphone after the 5 and 10 mg doses are lower than those observed following the 20 mg dose, although not statistically different. The oxymorphone oral clearance (CL/F) values following the 5 and 10 mg doses reflect the observed AUC differences.

Multiple dose:

Mean (SD) steady-state pharmacokinetic parameters :

Variable	5 mg q 6 hr	10 mg q 6 hr	20 mg q 6 hr
OXM			
AUCss (ng•hr/mL)	**4.63 (1.49)**	**10.19 (3.34)**	**21.10 (7.59)**
Cmax (ng/mL)	**1.73 (0.62)**	**3.51 (0.91)**	**7.33 (2.93)**
Cmin (ng/mL)	0.49 (0.17)	1.16 (0.43)	2.47 (0.94)
Tmax (hr)[a]	0.50 (0.25-6.00)	0.50 (0.25-1.00)	0.50 (0.25-1.50)
Cavg (ng/mL)	0.77 (0.25)	1.70 (0.56)	3.52 (1.27)
CL/F (L/min)	19.23 (4.27)	17.63 (4.42)	17.68 (6.14)
FI	1.62 (0.45)	1.46 (0.49)	1.39 (0.42)
R	2.41 (0.73)	2.54 (0.83)	2.34 (0.71)
6-OH-OXM			
AUCss (ng•hr/mL)	4.98 (2.07)	10.77 (4.21)	23.68 (10.14)
Cmax (ng/mL)	1.55 (0.52)	3.12 (1.08)	6.94 (2.86)
Cmin (ng/mL)	0.70 (0.33)	1.52 (0.71)	3.34 (1.45)
Tmax (hr)[a]	0.50 (0.25-0.50)	0.50 (0.25-1.00)	0.50 (0.25-1.50)
Cavg (ng/mL)	0.83 (0.35)	1.80 (0.70)	3.95 (1.69)
FI	1.12 (0.40)	0.97 (0.37)	0.94 (0.38)
R	3.49 (1.90)	3.44 (0.96)	3.43 (1.11)
OXM-3-G			
AUCss (ng•hr/mL)	618.77 (114.59)	1321.37 (226.44)	2557.29 (463.87)
Cmax (ng/mL)	180.25 (32.96)	376.25 (69.62)	722.24 (143.62)
Cmin (ng/mL)	59.67 (14.75)	136.77 (31.32)	272.54 (61.04)
Tmax (hr)[a]	1.00 (0.50-1.50)	1.00 (1.00-1.50)	1.00 (1.00-2.00)
Cavg (ng/mL)	103.13 (19.10)	220.23 (37.74)	426.22 (77.31)
FI	1.18 (0.21)	1.09 (0.24)	1.06 (0.24)
R	1.84 (0.33)	1.95 (0.38)	1.91 (0.36)
a: median (range)			
OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone; OXM-3-G=oxymorphone-3-glucuronide; FI=fluctuation (index);			
R=accumulation ratio			

The mean steady-state plasma concentrations of all three analytes progressively increase with increasing dose. Mean (SD) elimination half-life following a single 20 mg dose was 9.43 (3.36), 18.35 (5.77), and 9.67 (2.71) for oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide, respectively. The mean (SD) effective half-life calculated at the 20 mg every 6 hour dosage level was 7.43 (3.05), 12.05 (4.68), and 5.57 (1.57) for oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide, respectively. The mean (SD) oxymorphone clearance (CL/F) was 19.23 (4.27), 17.63 (4.42), and 17.68 (6.14) L/min following administration of 5, 10, and 20 mg of EN32003 every 6 hours, respectively.

Steady-state proportionality was assessed following normalization of the pharmacokinetic variables to a 10 mg dose rather than the protocol-specified 5 mg. Log-transformed results were then compared across treatment groups.

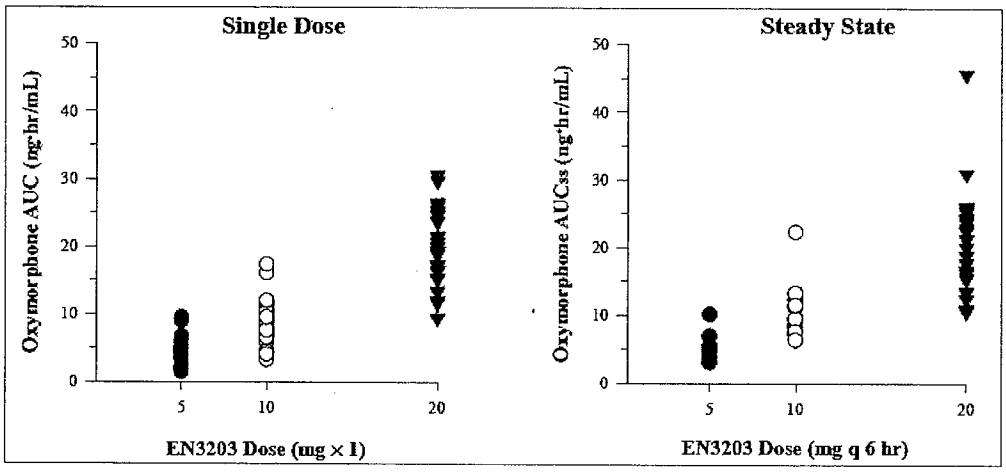
Analysis of Dose Proportionality at Steady-State Normalized to 10 mg:

Parameter	5 mg q 6 hr	10 mg q 6 hr	20 mg q 6 hr	p-value
OXM				
ln-AUCss (ng•hr/mL)	8.91 (1.03)	9.76 (1.03)	9.97 (1.03)	0.0600
ln-Cmax (ng/mL)	3.31 (1.05)	3.41 (1.05)	3.44 (1.05)	0.8338
ln-CL/F (L/min)	18.70 (1.03)	17.08 (1.03)	16.72 (1.03)	0.0600
6-OH-OXM				
ln-AUCss (ng•hr/mL)	9.14 (1.04)	9.99 (1.04)	10.83 (1.04)	0.0169
ln-Cmax (ng/mL)	2.91 (1.04)	2.94 (1.04)	3.19 (1.04)	0.1935
OXM-3-G				
ln-AUCss (ng•hr/mL)	1219.7 (1.02)	1306.5 (1.02)	1260.9 (1.02)	0.0347
ln-Cmax (ng/mL)	356.4 (1.01)	372.2 (1.01)	356.8 (1.01)	0.0339
OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone; OXM-3-G=oxymorphone-3-glucuronide				

Following dose-normalization, there were no statistically significant differences across the three treatment groups for oxymorphone, AUCss, Cmax, or CL/F. This analysis confirms that the pharmacokinetics of oxymorphone are both linear and dose proportional at steady-state. Similar findings were observed for the metabolites.

Comparison of Single-Dose and Steady-State AUC

The results observed for steady-state AUC are very close to the results estimated for AUC following a single dose, indicating that the steady-state pharmacokinetics are linear and can be predicted from single-dose data.



Single dose:

Variable	EN3203 (5 mg)	EN3203 (10 mg)	EN3203 (20 mg)
OXM			
AUC (ng•hr/mL)	**4.48 (2.07)**	**9.10 (3.40)**	**20.07 (5.80)**
AUCT (ng•hr/mL)	2.77 (1.40)	6.76 (3.18)	17.67 (5.76)
AUC0-6 (ng•hr/mL)	2.11 (1.00)	4.28 (1.49)	9.29 (3.04)
Cmax (ng/mL)	**1.10 (0.55)**	**1.93 (0.75)**	**4.39 (1.72)**
Tmax (hr)[a]	0.50 (0.25-1.00)	0.50 (0.25-1.50)	0.50 (0.25-1.00)
CL/F (L/min)	23.53 (13.18)	21.42 (9.92)	18.21 (6.16)
λz (hr-1)	0.1534 (0.1308)	0.1257 (0.0997)	0.0835 (0.0331)
t½ (hr)	7.25 (4.40)	7.78 (3.58)	9.43 (3.36)

Multiple dose:

Variable	5 mg q 6 hr	10 mg q 6 hr	20 mg q 6 hr
OXM			
AUCss (ng•hr/mL)	**4.63 (1.49)**	**10.19 (3.34)**	**21.10 (7.59)**
Cmax (ng/mL)	**1.73 (0.62)**	**3.51 (0.91)**	**7.33 (2.93)**
Cmin (ng/mL)	0.49 (0.17)	1.16 (0.43)	2.47 (0.94)
Tmax (hr)[a]	0.50 (0.25-6.00)	0.50 (0.25-1.00)	0.50 (0.25-1.50)
Cavg (ng/mL)	0.77 (0.25)	1.70 (0.56)	3.52 (1.27)
CL/F (L/min)	19.23 (4.27)	17.63 (4.42)	17.68 (6.14)
FI	1.62 (0.45)	1.46 (0.49)	1.39 (0.42)
R	2.41 (0.73)	2.54 (0.83)	2.34 (0.71)

AUCss : Area under the concentration versus time curve from time 0 to the end of one dosage interval at steady-state (i.e., time 0 to τ); calculated using linear trapezoid rule.

R (Accumulation Ratio) : calculated as AUC_{ss}/AUC_{0-6} or $C_{min(ss)}/C_{min(1)}$.

Safety

Typical adverse events were observed from the study.

Summary of Adverse Events (Events Reported by Two or More Subjects):

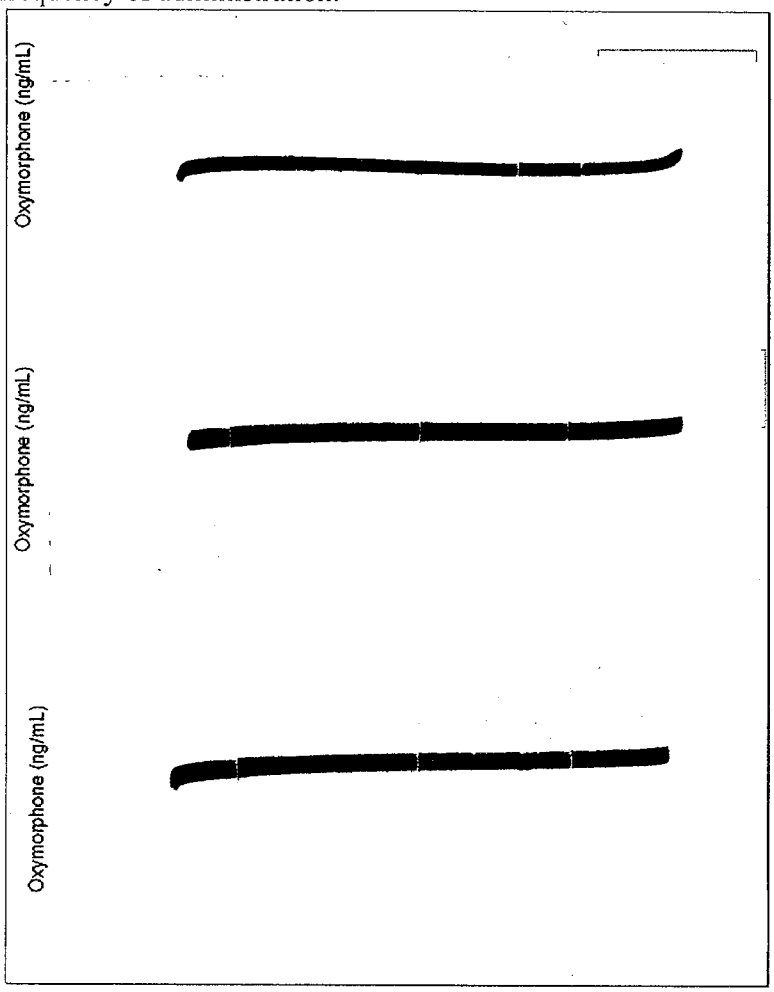
	EN3203 Dose		
	5 mg	**10 mg**	**20 mg**
Total Number of Subjects	23	23	24
Number with at least one AE	2 (8.7%)	1 (4.3%)	2 (8.3%)
Ear and labyrinth disorders	1 (4.3%)	0 (0.0%)	0 (0.0%)
-Ear pain	1 (4.3%)b, d	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	0 (0.0%)	0 (0.0%)	2 (8.3%)
-Nausea	0 (0.0%)	0 (0.0%)	1 (4.2%)a,
-Vomited	0 (0.0%)	0 (0.0%)	1 (4.2%)a,
-Dry mouth	0 (0.0%)	0 (0.0%)	1 (4.2%)a,
General disorders and administration site conditions	0 (0.0%)	1 (4.3%)	0 (0.0%)
-Chest pain	0 (0.0%)	1 (4.3%)a, d	0 (0.0%)
Nervous system disorders	1 (4.3%)	0 (0.0%)	1 (4.2%)
-Headache	1 (4.3%)a, d	0 (0.0%)	0 (0.0%)
-Dizzy	0 (0.0%)	0 (0.0%)	1 (4.2%)a,

aMild adverse event; bModerate adverse event; cPossibly related to medication; dUnlikely related to medication

2.2.1.2 What results are available for the 4- and 8-hour dosing simulations for the oxymorphone IR tablets?

Using the information obtained from Study EN3203-006, the Applicant conducted a simulation study to examine the 4- and 8-hour dosing regimen. Administration of oxymorphone immediate-release tablets has been recommended at 4 to 6- hourly intervals; and during as needed use, 20 mg doses were observed to be used on an 8-hourly dosage interval. The steady-state pharmacokinetics of oxymorphone have been studied when administered in a 6-hourly regimen, but not during 4- or 8-hourly administration. Steady-state concentrations were simulated from single-dose concentrations using the superposition method. Concentrations between existing time points were estimated by linear interpolation. It should be noted that modeling information (e.g., control files, data files, etc.) was not included in the Submission. The information from this modeling exercise should be considered as nice to know information at this time.

The following figure show simulated steady-state oxymorphone plasma concentrations by dose and frequency of administration.



As expected, at each dosage level, the 4-hourly regimen had higher and the 8-hourly regimen had lower maximum, minimum and average plasma concentrations than the 6-hourly regimen.

Percent Difference in Simulated Cmax and Daily Dose by Regimen:

	Regimen		
Parameter/Dose	**q 4 hr vs q 6 hr**	**q 6 hr vs q 8 hr**	**q 4 hr vs q 8 hr**
Cmax (ng/mL)			
5 mg	10.77%	3.88%	15.06%
10 mg	17.72%	13.20%	33.26%
20 mg	18.86%	11.62%	32.68%
Daily Dose	50%	33%	100%

Increasing the frequency of administration from 8-hourly to 4-hourly results in a 100% increase in total daily dose, but a lower than proportional increase in Cmax. The percent increase in Cmax results when shortening the dosage interval from 8-hourly to 4-hourly is 15.06%, 33.26%, and 32.68% for the 5, 10, and 20 mg doses, respectively.

The following table show simulated Steady-State Oxymorphone Pharmacokinetic Parameters by Dosage Regimen (Computed by Superposition). As expected, the predicted values for AUCss were essentially identical across dosage interval and within dosage level.

		Regimen	
Variable/Dose	**q 4 hr**	**q 6 hr**	**q 8 hr**
Cmax (ng/mL)			
5 mg	1.350	**1.219**	1.173
10 mg	2.966	**2.519**	2.226
20 mg	7.122	**5.992**	5.368
Cmin (ng/mL)			
5 mg	0.395	**0.266**	0.125
10 mg	1.243	**0.783**	0.466
20 mg	3.167	**1.974**	1.285
Cavg (ng/mL)			
5 mg	0.711	**0.474**	0.366
10 mg	1.892	**1.261**	0.946
20 mg	4.598	**3.065**	2.305
AUCss (ng•hr/mL)			
5 mg	2.844	**2.844**	2.926
10 mg	7.568	**7.568**	7.568
20 mg	18.392	**18.392**	18.443

Additional analysis: 'Modeling Simulation Validation' by comparison of 6 hour Study EN3203-006 values vs. 6 hour simulation values

Note that in Study 006, 5 mg and 10 mg blood oxymorphone concentrations at some blood sampling time-points were erratic. Thus, only "reliable" information is considered from 20 mg oxymorphone dosing.

The simulated Cmax concentrations were 1.219, 2.519, and 5.992 ng/mL for the 5, 10, and 20 mg doses administered every 6 hours. The corresponding Cmax concentrations, observed from the average plasma concentration data in Study EN3203-006, were 1.622, 3.256, and 6.951 ng/mL, respectively.

Simulated Steady-State oxymorphone PK parameters q 6 hr values:

		Regimen	
Variable	**5 mg q 6 hr**	**10 mg q 6 hr**	**20 mg q 6 hr**
Cmax (ng/mL)	**1.219**	**2.519**	**5.992**
Cmin (ng/mL)	0.266	0.783	1.974
Cavg (ng/mL)	0.474	1.261	3.065
AUCss (ng•hr/mL)	2.844	7.568	18.392

Study EN3203-006 Steady-State Oxymorphone PK Parameters

		Regimen	
Variable	**5 mg q 6 hr**	**10 mg q 6 hr**	**20 mg q 6 hr**
Cmax (ng/mL)	**1.622**	**3.256**	**6.951**
Cmin (ng/mL)	0.490	1.158	2.456
Cavg (ng/mL)	0.771	1.698	3.516
AUCss (ng•hr/mL)	4.626	10.188	21.099

Simulated/Actual oxymorphone parameter ratio:

		Regimen	
Variable	**5 mg q 6 hr**	**10 mg q 6 hr**	**20 mg q 6 hr**
Cmax (ng/mL)	**0.75**	**0.77**	**0.86**
Cmin (ng/mL)	0.53	0.68	0.80
Cavg (ng/mL)	0.61	0.74	0.87
AUCss (ng•hr/mL)	0.61	0.74	0.87

The Cmax ratios of predicted/observed were **0.75, 0.77, and 0.86** for the 5, 10, and 20 mg doses, respectively. That is, based on Cmax, the simulated (predicted by superposition) average steady-state plasma concentrations underestimated 25, 23, and 14% for 5, 10, and 20 mg doses, respectively, compared to that of the observed values from Study EN3202-006. Again, due to the fact that some of the blood concentrations in the 5 and 10 mg treatment groups were near the limit of detection in Study EN3203-006, 5 and 10 mg data should be taken with caution. It is expected that similar results may be obtained from 4- and 8-hour dosing regimens.

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_____ Draft Labeling

_____ Deliberative Process

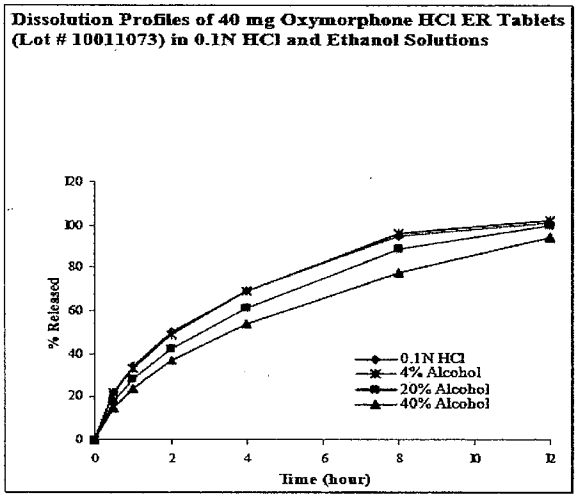
Withheld Track Number: Clin Pharm/Bio-_____

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

In vitro dissolution study (Document No. ENDO-2436-01)

In vitro dissolution profiles of 40 mg oxymorphone hydrochloride ER tablets were compared in 0.1 N HCl and ethanol/0.1 N HCl solutions at 4%, 20% and 40% ethanol concentrations. The results of this study on the extended-release formulation did not indicate a potential for product dose dumping in the presence of alcohol. The tablets were intact throughout the dissolution tests in all media. The release rate correlates inversely with the amount of ethanol. The similarity factors relative to the 0.1N HCl medium are ——— for the 4%, 20% and 40% ethanol solutions, respectively.



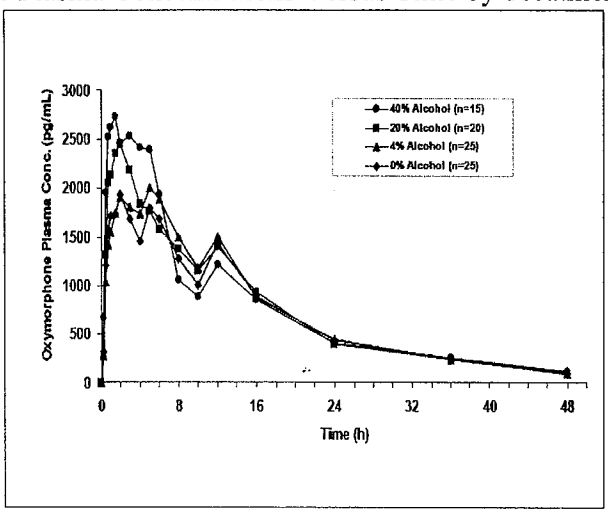
Similarity Factor (f_2) for Dissolution Profiles of 40 mg Oxymorphone HCl ER Tablets in 0.1N HCl and Ethanol Solutions

	f2		
Medium	4% Ethanol	20% Ethanol	40% Ethanol
Rel. to 0.1 N HCl	—	—	—

In vivo alcohol interaction study (Study EN3202-033)

This was an open-label, randomized, single-dose, four-period crossover design. Twenty-eight subjects were randomly allocated to receive a single dose of EN3202 40 mg ER co-administered with 240 mL of either an ethanol solution or water over four periods, with each period separated by a minimum 7-day washout period. All subjects received treatment under fasted conditions.

Mean Oxymorphone Plasma Concentrations Versus Time by Treatment):



Descriptive Statistics for Oxymorphone Pharmacokinetic Parameters by Treatment :

			Treatment (Treatment Code)		
		EN3202 40 mg + 40% Ethanol (A)	EN3202 40 mg + 20% Ethanol (B)	EN3202 40 mg + 4% Ethanol (C)	EN3202 40 mg + Water (D)
Parameter	Statistic	(n=15)	(n=20)	(n=25)	(n=25)
AUC0-t, pg•h/mL	Mean (SD)	36385 (12441)	35389 (11495)	35146 (12534)	33350 (11864)
AUC0-inf, pg•h/mL	**Mean (SD)**	**39973[a] (13595)**	**36889 (12356)**	**37551[b] (13452)**	**36034[b] (11388)**
Cmax, pg/mL	**Mean (SD)**	**3917 (1672)**	**3089 (1150)**	**2564 (1037)**	**2373 (870)**
Tmax, h	Median (Min-max)	1.5 (0.75 – 6.00)	1.5 (0.75 – 8.00)	3.0 (1.00 – 12.00)	2.0 (0.50 – 12.00)
t½, h	Mean (SD)	11.3[a] (3.5)	9.9 (3.2)	10.4[b] (4.1)	10.7[b] (4.7)
[a] n=13; [b] n=24					

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Statistical Analyses of Oxymorphone Pharmacokinetic Parameters Excluding Tmax

					Diff of LS Means	Ratio of Geo. Means	90% CI of the Ratio		P-Value	
Parameter	Trt	N	LS Meansb	Geo. Means	[-D]	[/D]	[/D]	Trt	Period	Seq
AUC[0-inf] (pg.hr/mL)	A	13	10.57	38763.92	0.12	**1.127**	(1.03, 1.24)	0.192	0.893	0.088
	B	20	10.46	34731.99	0.01	**1.010**	(0.93, 1.09)			
	C	24	10.47	35148.36	0.02	**1.022**	(0.95, 1.10)			
	D	24	10.45	34400.28						
AUC[0-t] (pg.hr/mL)	A	15	10.48	35710.93	0.12	**1.129**	(1.03, 1.24)	0.217	0.757	0.037
	B	20	10.40	32891.74	0.04	**1.040**	(0.95, 1.13)			
	C	25	10.42	33373.54	0.05	**1.055**	(0.97, 1.14)			
	D	25	10.36	31636.53						
Cmax (pg/mL)	A	15	8.243	3799.564	0.533	**1.703**	(1.476, 1.966)	<.001	0.742	0.114
	B	20	7.979	2918.795	0.269	**1.309**	(1.151, 1.488)			
	C	25	7.780	2393.368	0.070	**1.073**	(0.952, 1.209)			
	D	25	7.710	2230.474						

*a*Treatment: A = EN3202 40 mg + 240 mL of 40% ethanol, B = EN3202 40 mg + 240 mL of 20% ethanol, C = EN3202 40 mg + 240 mL of 4% ethanol, D = EN3202 40 mg + 240 mL of water (0% ethanol).
*b*LS Means for AUC[0-t], AUC[0-inf] and Cmax are on the logarithm scale. LS means for Lambda_z and T1/2 are on the original scale.
ANOVA=analysis of variance; CI=confidence interval; Diff=difference; Geo=geometric; LS=least squares; Seq=sequence; Trt=treatment.
Note: An ANOVA model was performed on Lambda_z, T1/2 and the natural logarithms of AUC[0-t], AUC[0-inf] and Cmax. The model included sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect. Point estimates and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

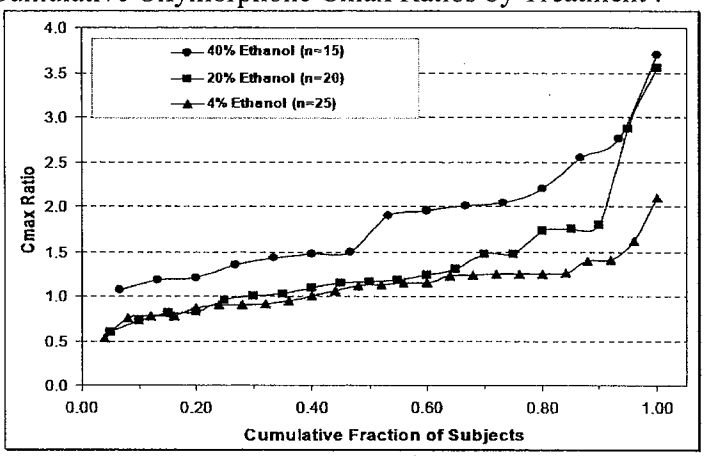
- The geometric mean ratio showed that AUC was 13% higher for the 40% alcohol treatment group compared to the 0% alcohol treatment group. This was non-statistically significant.

- There was a statistically significant effect of treatment on Cmax ($p<0.001$). The geometric mean ratios showed that Cmax was 70%, 31%, and 7% higher for the 40% (A), 20% (B) and 4% (C) ethanol treatments, respectively, compared to the 0% ethanol treatment (D).

- Individual subject Cmax ratios for the 40% (A), 20% (B) and 4% (C) ethanol treatments, versus the 0% ethanol treatment (D) are plotted below. These ratios are shown as the cumulative fraction of subjects within a treatment. For example, for the 40% ethanol treatment (A), one-half of the subjects had a Cmax ratio below 1.5; 0.8 (80%) of the subjects had a Cmax ratio below 2.2. The Cmax ratio for the 40% ethanol treatment (A) was consistently higher than the other two ethanol treatments. The 20% ethanol treatment (B) did not diverge from the 4% ethanol treatment (C) until a cumulative fraction of approximately 0.65, and a

large divergence was only seen for the last two subject values (cumulative fraction above 0.92).

Cumulative Oxymorphone Cmax Ratios by Treatment :



- Vomiting was the most frequently occurring TEAE, and its incidence increased as the ethanol solution percentage increased. Ten of 26 subjects (39%) reported vomiting during 40% alcohol treatment, compared with 6 of 28 subjects (21%) during 20% alcohol treatment, and 1 of 28 subjects (4%) during 4% alcohol treatment. No subject reported vomiting during 0% alcohol treatment. Other frequently occurring TEAEs included headache, nausea and dizziness. Headache was reported by 4 of 26 subjects (15%) during 40%, 4 of 28 subjects (14%) during 20%, 3 of 28 subjects (11%) during 4% and 2 of 25 subjects (8%) during 0% treatments.

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

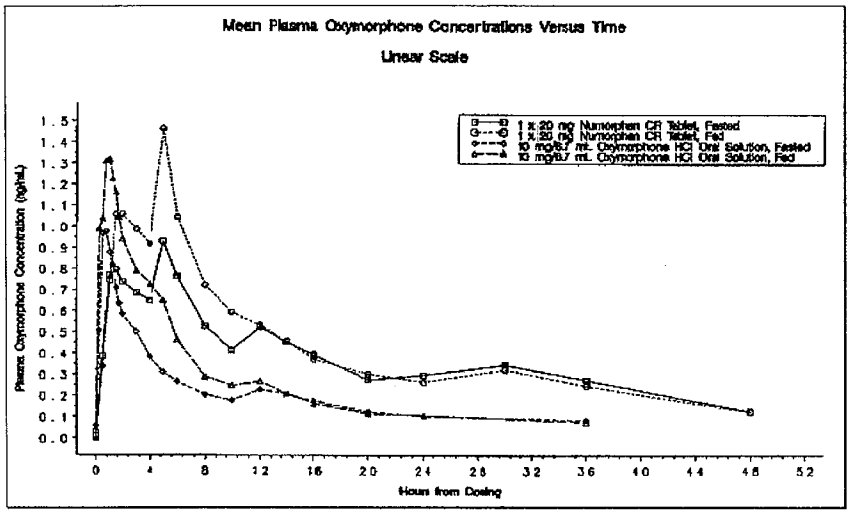
Study EN3202-003

This study was a Phase I, randomized, single-dose, fed-fasted, four-way crossover bioavailability study using Oxymorphone ER (20 mg) tablet and Oxymorphone Oral solution (10 mg). Subjects were either fasted overnight or given a standardized high-fat meal. All treatments were taken with 240 mL of water.

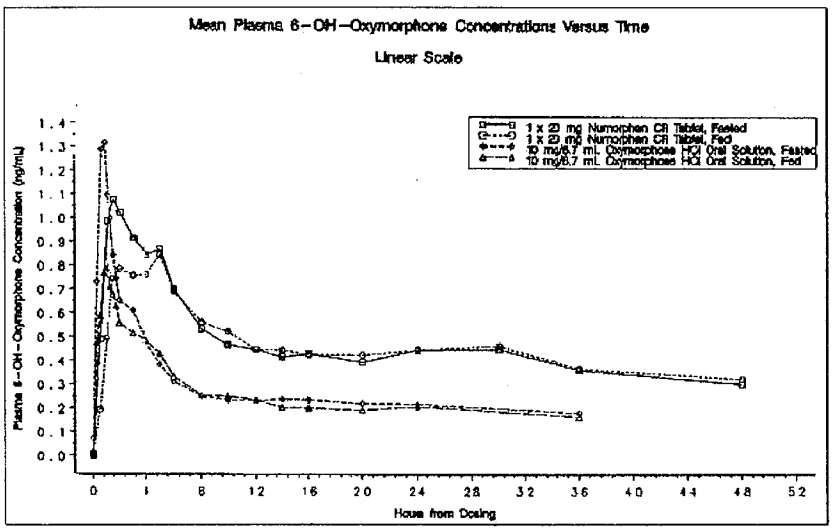
Treatment Group	Oxymorphone Formulation	Dose	Food
A	ER	20 mg	Fasted
B	ER	20 mg	Fed
C	Solution*	10 mg	Fasted
D	Solution*	10 mg	Fed

*Oxymorphone HCl, USP, 1.5 mg/mL injection 10 mL vials

The mean oxymorphone concentration profile is presented below.



The mean 6-OH-oxymorphone concentration profile is presented below.



For 20 mg ER tablet, with food, oxymorphone Cmax and AUC values increased 58% and 18%, respectively. For 10 mg oxymorphone solution, with food, Cmax and AUC values increased 50% and 32%, respectively.

For 20 mg ER tablet, with food, 6-OH-oxymorphone Cmax and AUC values decreased and increased 9% and 9%, respectively. For 10 mg oxymorphone solution, with food, 6-OH-oxymorphone Cmax and AUC values decreased and increased 35% and 6%, respectively.

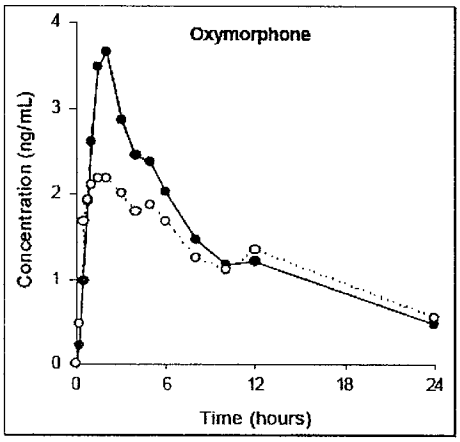
Study EN3202-008

This study was a Phase I, randomized, single-dose, fed-fasted, four-way crossover bioavailability study using Oxymorphone ER (40 mg) tablet and Oxymorphone IR (4x10mg). Subjects were either fasted overnight or given a standardized high-fat meal. All treatments were taken with 240 mL of water.

Treatment Group	Oxymorphone Formulation	Dose	Food
A	ER	40 mg	Fasted
B	ER	40 mg	Fed
C	IR*	40 mg	Fasted
D	IR*	40 mg	Fed

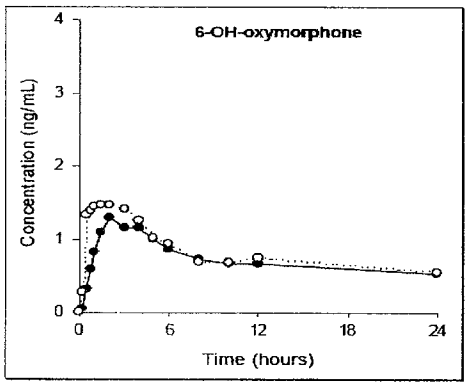
*IR : 4 x10 mg tablets

The mean oxymorphone concentration profile for 40 mg ER is presented below.



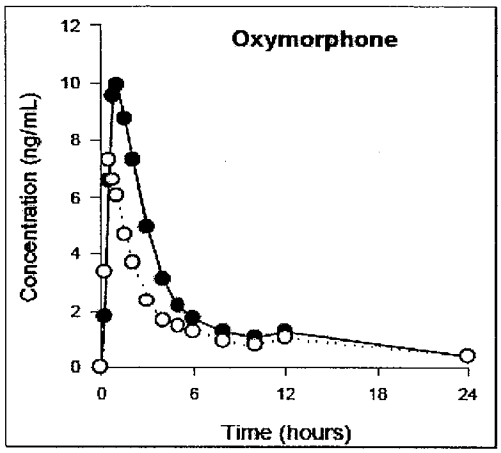
Solidd dark circle : EN2002 ER Fed; Open circle : EN2002 ER Fasting

The mean 6-OH-oxymorphone concentration profile for 40 mg ER is presented below.



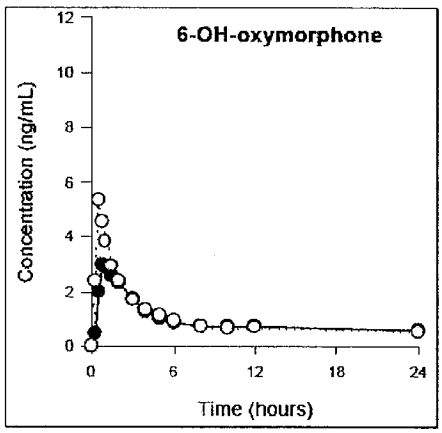
Solid dark circle : EN2002 ER Fed; Open circle : EN2002 ER Fasting

The mean oxymorphone concentration profile for 4x10 mg IR is presented below.



Solid dark circle : EN2003 IR Fed; Open circle : EN2003 IR Fasting

The mean 6-OH-oxymorphone concentration profile for 4x10 mg IR is presented below.



Solid dark circle : EN2003 IR Fed; Open circle : EN2003 IR Fasting

For 40 mg ER tablet, with food, oxymorphone Cmax value increased 51%, however, oxymorphone AUC did not change with food. For 40 mg ER tablet, with food, 6-OH-oxymorphone Cmax value decreased 14%, however, 6-OH-oxymorphone AUC did not change with food.

For 4x10 mg IR tablet, with food, both oxymorphone Cmax and AUC values increased 38%. For 4x10 mg IR tablet, with food, 6-OH-oxymorphone Cmax value decreased 37%, however, 6-OH-oxymorphone AUC did not change with food.

The findings from above two studies confirmed the information found in the original NDA.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the submitted studies?

Study 003

An LC/MS/MS method was developed and validated for the determination of oxymorphone and 6-OH oxymorphone in human EDTA plasma. Samples were analyzed with Perkin Elmer Sciex API III+, or equivalent using a turbo ion spray interface, was employed in this study. Positive ions were monitored in the MRM mode. A typical inter-day precision and accuracy information is presented below:

Interday Precision and Accuracy - Oxymorphone

	QC 0.1500 ng/mL	QC 3.000 ng/mL	QC 15.000 ng/mL
Mean	0.1367	2.8610	13.7592
C.V.%	5.93	3.50	14.23
R.E.%	-8.87	-4.63	-8.27
N	53	54	52

Interday Precision and Accuracy - 6-OH Oxymorphone

	QC 0.1500 ng/mL	QC 3.000 ng/mL	QC 15.000 ng/mL
Mean	0.1421	2.9280	13.9751
C.V.%	10.70	9.51	14.45
R.E.%	-5.27	-2.40	-6.83
N	53	54	52

Study 008

Similar to Study 003, this study used LC/MS/MS method. A typical inter-day precision and accuracy information is presented below:

Parameter	OXM	6-OH-OXM	OXM-3-G
Number of Runs	28	29	28
Linearity (mean r)	[redacted]		
Inter-day Precision (%CV)*			
Inter-day Accuracy (%Actual)*			

*precision and accuracy results based on QC samples excluding dilutions OXM = oxymorphone 6-OH-OXM = 6-OH-oxymorphone OXM-3-G = oxymorphone-3-glucuronide

3 Detailed Labeling Recommendations

The following recommendation is made to the Clinical Pharmacology, Pharmacokinetic sections of the Labeling. Texts are ~~deleted~~ and added (in red fonts). In most parts, the Applicant's suggestion is acceptable. Similar language should be used in both IR and ER package inserts.

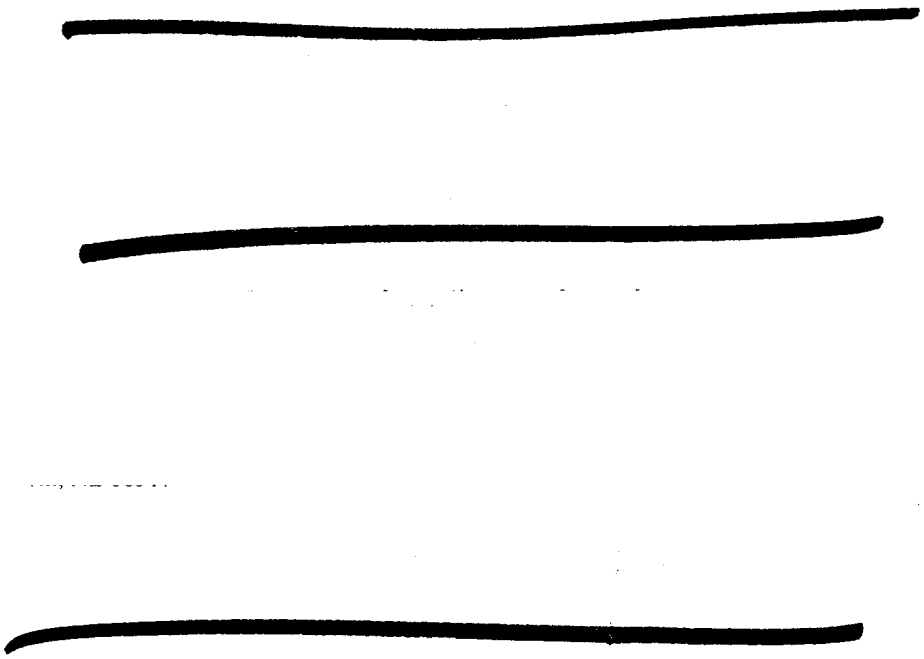
28 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____



4.2 Individual Study Review

4.2.1 In vitro dissolution study (Document No. ENDO-2436-01; Submitted to the IND56,919 Serial No. 207)

In vitro dissolution profiles of 40 mg oxymorphone hydrochloride ER tablets were compared in 0.1 N HCl and ethanol/0.1 N HCl solutions at 4%, 20% and 40% ethanol concentrations. The release profiles of Oxymorphone Hydrochloride ER tablets have been previously studied in several dissolution media including 0.1 N HCl, pH 4.5 and pH 6.8 Phosphate buffer (Endo report Doc. No. ENDO-1672). A medium of 900 mL of pH 4.5 Phosphate buffer was recommended by the Agency for QC control testing and was filed in original NDA 21-610. The NDA method was linked to an earlier dissolution method using 500 mL of 0.1N HCl medium (Endo report Doc. No. ENDO-1917). In consideration of ethanol mediated dose dumping, a potential immediate release of the drug should most likely occur in the acidic milieu of the stomach. Therefore, a study was performed in 500 mL of solutions containing 4%, 20% and 40% ethanol in 0.1 N HCl, and in 500 mL of 0.1 N HCl medium for comparison.

The dissolution samples were analyzed by an HPLC method. The HPLC method for the determination of dissolution samples was similar to that of the NDA method, however, the mobile phase composition and column temperature were modified to accommodate

the solvent strength changes due to the presence of ethanol. Specificity, linearity, accuracy and precision of the method were re-validated against criteria set forth in Endo SOP, "Analytical Method Validation", ENDO-0966.

Experimental Setup:

Instruments
[redacted] HPLC 1100 series with a UV detector
[redacted] Dissolution System 2100A and 2100

Dissolution Conditions	
Apparatus:	II (Paddle), 50 rpm
Sampling times for profile:	0.5, 1, 2, 4, 8, and 12 hours
Medium:	500 mL, 37 ± 0.5° C
	(1) 0.1 N HCl
	(2) 4% ethanol in 0.1N HCl
	(3) 20% ethanol in 0.1N HCl
	(4) 40% ethanol in 0.1N HCl

HPLC Conditions for Analysis of Dissolution Samples	
Column:	[redacted]
Flow Rate	[redacted]
Column Temperature:	[redacted]
Detector:	[redacted]
Injection Volume:	[redacted]
Run Time:	[redacted]
Approximate Retention Time:	
Oxymorphone	9.5 minutes (approximately)

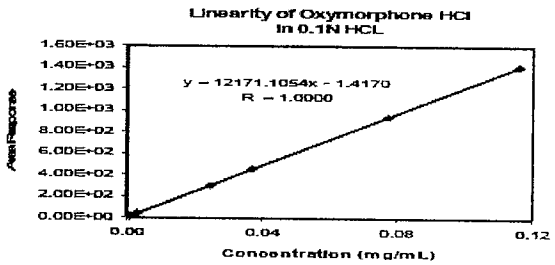
The results of this study on the extended-release formulation did not indicate a potential for product dose dumping in the presence of alcohol.

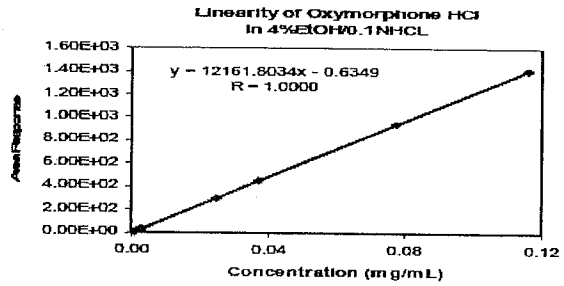
RESULTS AND DISCUSSIONS

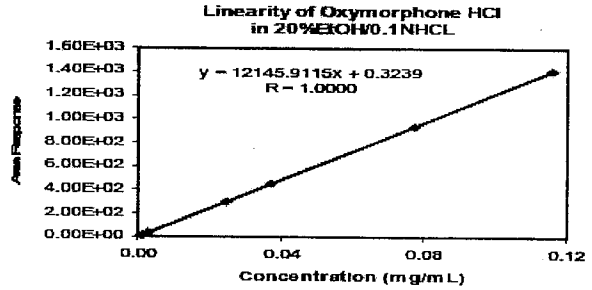
1. Method Validation

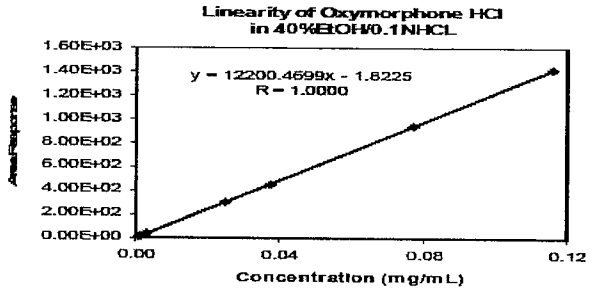
a. The specificity of the HPLC method was demonstrated by the absence of medium and placebo interferences with the determination of Oxymorphone HCl.

b. The Linearity of Oxymorphone response was demonstrated from 1% to 145% of the nominal sample concentration (0.08 mg/mL) in 0.1 N HCl, 4% ethanol, 20% ethanol and 40% ethanol solutions. The linear regression correlation coefficients were all 1.000 and the intercepts ranged from 0.03% to 0.19%.







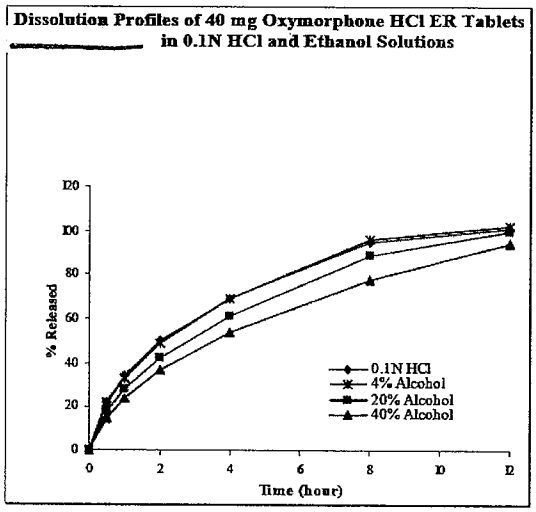


c. The accuracy of the method was demonstrated by recovering Oxymorphone HCl equivalent to 10%, 100% and 120% of 40 mg from the placebo powder in 0.1N HCl, 4% ethanol, 20% ethanol and 40% ethanol solutions. The overall mean recovery (n=9) was 101.0%, 99.4%, 99.8% and 99.5% for 0.1N HCl, 4% ethanol, 20% ethanol and 40% ethanol solutions, respectively. The mean recovery at each level ranged from 96.7% to 102.8%. The precision of the method was demonstrated by the pooled %RSDs (Table 3) obtained in the accuracy study. The pooled %RSDs of 0.46, 0.60, 2.48 and 1.02 for 0.1N HCl, 4% ethanol, 20% ethanol and 40% ethanol solutions, respectively.

Replicate Spls. in Solutions of	% Recovery of Oxymorphone HCl at Levels of			Overall Mean (%)	Pooled %RSD
	1.25%	25%	120%		
0.1 N HCl					
1	101.0	102.2	100.2	**101.0**	**0.46**
2	101.5	100.7	100.5		
3	101.4	101.4	100.3		
Mean	101.3	101.4	100.3		
%RSD	0.26	0.74	0.15		
4% Ethanol					
1	97.5	99.4	100.7	**99.4**	**0.60**
2	99.3	99.5	100.2		
3	98.9	99.5	99.9		
Mean	98.6	99.5	100.3		
%RSD	0.96	0.06	0.40		
20% Ethanol					
1	103.0	98.8	100.4	**99.8**	**2.48**
2	95.0	99.4	100.4		
3	101.6	99.1	100.1		
Mean	99.9	99.1	100.3		
%RSD	4.28	0.30	0.17		
40% Ethanol					
1	102.4	95.8	98.8	**99.5**	**1.02**
2	103.1	95.8	99.6		
3	102.9	98.6	98.9		
Mean	102.8	96.7	99.1		
%RSD	0.35	1.67	0.44		

2. Dissolution profile

- The tablets were intact throughout the dissolution tests in all media. The data indicates that the release rate correlates inversely with the amount of ethanol.
- The similarity factors relative to the 0.1N HCl medium are _____ for the 4%, 20% and 40% ethanol solutions, respectively.



Means of Dissolution Profile of 40 mg Oxymorphone HCl ER Tablets in 0.1N HCl and Ethanol Solutions

Mean % Released (n=12)							
Time Point	0	0.5	1	2	4	8	12
0.1N HCl	0	22	34	50	69	95	101
%RSD	0	6.1	3.3	3.0	1.9	1.6	1.9
Range	0						
4% EtOH	0	22	33	49	69	96	102
%RSD	0	3.3	3.0	2.5	2.0	1.6	1.8
Range	0						
20% EtOH	0	18	28	42	61	89	100
%RSD	0	2.1	2.4	2.5	2.9	2.0	1.9
Range	0						
40% EtOH	0	15	24	37	54	78	94
%RSD	0	6.0	2.2	1.8	1.9	2.3	3.2
Range	0						

Similarity Factor (f_2) for Dissolution Profiles of 40 mg Oxymorphone HCl ER Tablets in 0.1N HCl and Ethanol Solutions

	f2		
Medium	4% Ethanol	20% Ethanol	40% Ethanol
Rel. to 0.1 N HCl			

4.2.2 In Vivo Alcohol study -

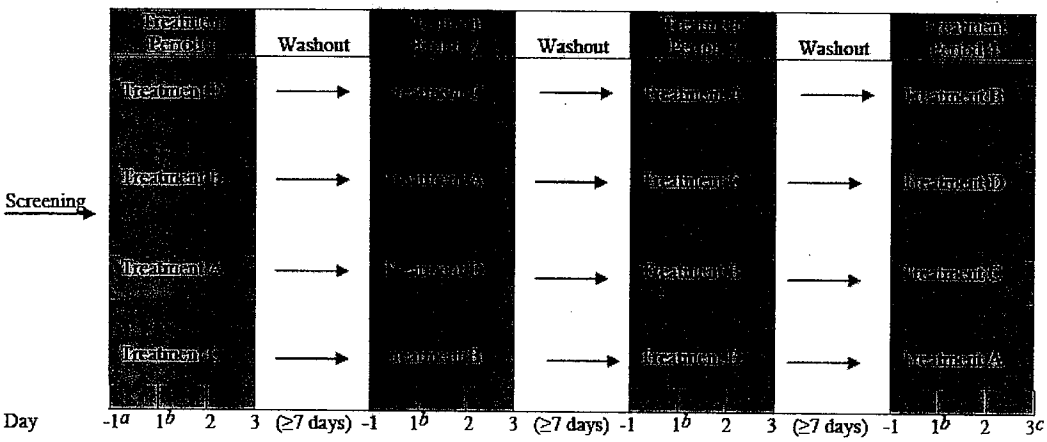
Study EN3202-033 Alcohol-Interaction

STUDY OBJECTIVE
The study objective was to determine the single-dose bioavailability (rate and extent of absorption) of EN3202 40 mg when co-administered with different concentrations of ethanol compared with water under fasted conditions.

Overall Study Design
This study was conducted using an open-label, randomized, single-dose, four-period crossover design. Twenty-eight subjects were randomly allocated to receive a single dose of EN3202 40 mg co-administered with either an ethanol solution or water over four periods, with each period separated by a minimum 7-day washout period. All subjects received treatment under fasted conditions. The four treatments were:
A EN3202 40 mg + 240 mL of 40% ethanol
B EN3202 40 mg + 240 mL of 20% ethanol
C EN3202 40 mg + 240 mL of 4% ethanol
D EN3202 40 mg + 240 mL of water (0% ethanol)

Subjects were confined to the clinical research facility starting the evening prior to dosing (Day – 1) through the morning of Day 3 (48 hours after the administration of the EN3202 40-mg tablet) of each treatment period. Blood samples for oxymorphone plasma concentration determination and pharmacokinetic analyses were obtained at regular intervals through 48 hours after the administration of the EN3202 40-mg tablet.

To protect subjects from potential opioid-related adverse events (AEs), the opiate antagonist naltrexone HCl (50 mg) was administered approximately 12 hours and 2 hours before the administration of EN3202 in each treatment period. An additional dose of naltrexone 50 mg was administered 12 hours after EN3202 dosing in each treatment period.



[a]Subjects randomized to treatment sequence.
[b]Single dose of study treatment administered.
[c]End of study assessments.
Treatment A=EN3202 40 mg + 240 mL 40% ethanol solution; Treatment B=EN3202 40 mg + 240 mL 20% ethanol solution; Treatment C=EN3202 40 mg + 240 mL 4% ethanol solution; Treatment D=EN3202 40 mg + 240 mL of water (0% ethanol solution).
Note: Naltrexone 50 mg administered 12 hr and 2 hr prior to study treatment and 12 hr after study treatment in each treatment period.

Discussion of the Study Design

The crossover design is standard for bioavailability studies and permits a direct comparison of the three different combinations of EN3202 40 mg plus ethanol solution to EN3202 40 mg plus water within the same subject. A randomized design was chosen to ensure that the study results would be unbiased. Blinding of treatment assignment was not necessary since the primary endpoints were based on an objective measure (i.e., plasma oxymorphone concentrations).

Subjects were considered susceptible to all of the potential opioid-related pharmacological effects of oxymorphone, including respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, or shock. Because naltrexone 50 mg is known to block the pharmacological effects of opioids for as long as 24 hours (Naltrexone Package Insert, 2002, Gonzales and Brogden, 1988), it was administered at three time points during each treatment period: 12 hours and 2 hours before EN3202 administration and 12 hours after EN3202 administration. This schedule for naltrexone dosing provided adequate protection from potential opioid-related AEs, and allowed the investigator the opportunity to observe subjects for any AEs associated with naltrexone prior to administering study medication.

Intravenous (IV) naloxone was also available for administration, if necessary, following study treatment administration. In addition, advanced cardiac life support (ACLS) equipment and ACLS-certified personnel were available at the site throughout the entire study periods that subjects were confined to the clinical study unit.

Inclusion Criteria

Subjects were eligible for participation in the study if they:

Were healthy, non-smoking (defined as not having smoked or used nicotine-containing products on a regular basis for at least 6 months) male and female subjects, aged 21 to 45,

inclusive, as determined by medical history, physical examination, 12-lead electrocardiogram (ECG) and clinical laboratory evaluations
– If female, must have been using a medically acceptable form of contraception for at least 1 month before dosing (e.g., intrauterine device, hormonal birth control, or double barrier method). For the purpose of this study, all females were considered to be of childbearing potential unless they had been post-menopausal, biologically sterile, or surgically sterile (i.e., hysterectomy, bilateral oophorectomy, or tubal ligation) for more than 1 year
– Women of childbearing potential must have had a negative pregnancy test within 24 hours prior to the start of the study

Had a history of moderate ethanol consumption defined as consumption of 7-21 drinks per week for at least the past year (a drink is defined as 1½ oz liquor, one 12 oz can of beer, or one 5 oz glass of wine)

Had a body mass index (BMI) =18.5 and =32 kg/m2 unless jointly approved by the investigator and sponsor

Had a body weight of at least 57 kg (125 lbs) if male and 68 kg (150 lbs) if female

Had no significant diseases in the medical history or evidence of clinically significant findings on physical examination, clinical laboratory evaluations (hematology, serum chemistries, urinalysis) or 12-lead ECG

Were informed of the nature of the study and had provided written informed consent

Were able to communicate effectively with the study personnel

To prevent the potential occurrence of an acute abstinence syndrome resulting from naltrexone administration, potential study participants were carefully screened by the investigator to ensure that there was no reasonable possibility of recent opioid or prior opioid abuse. All potential study participants were informed of the risks associated with any recent opioid abuse.

Exclusion Criteria

Subjects were not enrolled in the study if any of the following exclusion criteria applied:

Known hypersensitivity or allergy to oxymorphone, other opioids, naltrexone, or ethanol

Women who were pregnant or breastfeeding

Any disease or condition that might have compromised the cardiovascular, hematological, renal, hepatic, pulmonary (including chronic asthma), endocrine (e.g. diabetes), central nervous, or gastrointestinal (GI) (including gastric ulcer) systems unless deemed not clinically significant jointly by the investigator and sponsor

Any disease or condition that may have interfered with ADME (absorption, distribution, metabolism, excretion) of study treatment or would place the subject at increased risk. This included variants and deficiencies of aldehyde dehydrogenase.

Elevated AST (aspartate aminotransferase [SGOT]), ALT (alanine aminotransferase [SGPT]), GGT (.-Glutamyltransferase), alkaline phosphatase, bilirubin, BUN (blood urea nitrogen), creatinine levels (>15% above the upper limit of normal reference range of the reporting laboratory); or hemoglobin level or hematocrit level below the lower limit of normal values (<15% below the lower limit of the normal reference range of the reporting laboratory), unless deemed not clinically significant jointly by the investigator and

sponsor; increased bilirubin levels resulting from a known history or clinical evidence of Gilbert's syndrome did not exclude subjects

Positive screen for Hepatitis B consisting of HBsAg (Hepatitis B Surface Antigen), anti-HCV (Hepatitis C Antibody), or HIV antibody

Received an investigational drug within 30 days prior to check-in on Day –1; for investigational drugs with an elimination half-life greater than 15 days, this was be extended to 60 days

Use of any medication (prescription or over-the-counter [OTC], such as antacids, multivitamins, aspirin, herbal preparations, and nutritional supplements) within 14 days prior to administration of study treatment, unless jointly approved by the investigator and sponsor; oral contraceptives were allowed

Use of a drug therapy known to induce or inhibit hepatic drug metabolism within 30 days prior to administration of study treatment

A positive urine screen for substances of abuse, including ethanol, cocaine, tetrahydrocannabinol (THC), barbiturates, amphetamines, benzodiazepines, phencyclidine (PCP), and opiates

History of ethanol abuse, illicit drug use, or serious mental illness

History of difficulty with phlebotomy procedures

Donated blood (>400 mL) or blood products within 45 days prior to study check-in on Day –1, Period 1

Febrile illness within 6 days of Day –1 of Period 1

Previously received study treatment (oxymorphone)

Identity of Investigational Product

EN3202 40-mg tablets were provided by the sponsor as open-label stock bottles containing 60 tablets per bottle. Commercially available ethanol (vodka, 80 proof) and commercially available naltrexone used in the study were obtained by the pharmacy department of the clinical research facility. The dosing solutions were prepared by diluting the vodka with water.

During each of the four treatment periods, each subject received a single oral dose of EN3202 40 mg in the morning on Day 1. Each EN3202 dose was co-administered with ethanol solution or water, with the concentration of ethanol determined by the randomization scheme. The treatments administered in the study were:

A EN3202 40 mg + 240 mL of 40% ethanol
B EN3202 40 mg + 240 mL of 20% ethanol
C EN3202 40 mg + 240 mL of 4% ethanol
D EN3202 40 mg + 240 mL of water (0% ethanol)

Study Medication and Other Treatments Administered

Treatment	Batch/Lot Number	Expiration Date
Study Medication		
EN3202 40-mg tablets	Batch #10011073	N/A
Other Treatments		
Naltrexone (ReVia®) 50-mg tabletsa	Lot #402753001T Lot #03-11 212	06/06None
Vodka, 80 proofb	5	

aManufactured by DuraMed Pharmaceuticals, Inc. (a division of Barr Pharmaceuticals, Inc.) in Woodcliff Lake, NJ.
bManufactured by Tito's Handmade Vodka in Austin, TX.
N/A=not applicable

Selection of Doses
The 40-mg dose of EN3202 is the highest single-dose strength of EN3202 to be marketed. This dose was therefore chosen in order to maximize the single-dose exposure to EN3202 in this study.

For each treatment period, the EN3202 40-mg tablet was taken at the start of dosing with the ethanol solution. Thereafter, subjects ingested the remaining 240 mL of solution as quickly as possible. If, however, the entire 240 mL of solution could not be ingested before scheduled pharmacokinetic sample collection time points, subjects had the samples drawn and then continued drinking the remainder of the solution. The time at which subjects finished the entire 240 mL solution was recorded in the CRF.

The study medication was administered after an overnight fast (at least 8 hours) and subjects remained fasting for at least 4 hours after treatment administration. Water was allowed as desired, except for 1 hour before and 1 hour after treatment administration (this restriction did not apply to the water contained in the dosing vehicle). Subjects were to remain in an upright posture (not recumbent; e.g., sitting or standing) for at least 1 hour following the completion of EN3202 dose administration.

On the evening of Day −1 of each treatment period (approximately 12 hours before study medication administration), subjects received a 50-mg naltrexone tablet. A second dose of naltrexone 50 mg was administered in the morning of Day 1 (approximately 2 hours before administration of study medication); a third dose of naltrexone 50 mg was administered 12 hours after study medication administration. Each naltrexone tablet was administered orally with 240 mL of drinking water (at room temperature), and subjects were instructed to drink all of the water. Intravenous naloxone, ACLS equipment, and ACLS-certified personnel (informed of the potential hazards associated with the study) were available at the site during each treatment period.

Restrictions on Study Subjects
Subjects were served standardized meals during the confinement periods (i.e., Day −1 to Day 3 of each treatment period) in the clinical research facility, and no other foods were permitted. The meals were served at approximately 4 and 10 hours after EN3202 was administered. All meals and beverages were to be xanthine-free and identical for each subject throughout the treatment periods. Water was permitted *ad libitum* throughout the study. Subjects were to refrain from excess physical activity throughout the duration of the study.

Blood Sample Collections
Samples of venous blood were obtained in 7 mL K3 EDTA tubes at: time 0 (pre-dose), 15.0 min, 30.0 min, 45.0 min, 1 hr, 1.5 hr, 2.0 hr, 3.0 hr, 4.0 hr, 5.0 hr, 6.0 hr, 8.0 hr, 10.0

hr, 12.0 hr, 16.0 hr, 24.0 hr, 36 hr, and 48 hr after administration of each EN3202 40-mg tablet.

Immediately after collection, the tube was to be gently inverted several times to mix the anticoagulant with the blood sample. The plasma fraction was separated by placing the collection tube into a refrigerated centrifuge (4–8°C) for 10 minutes at 1,500 × g. The plasma fraction was withdrawn by pipette and divided into two polypropylene freezing tubes (with each tube receiving approximately equal aliquots). All sample collection and freezing tubes were clearly labeled in a manner that identified the subject and the collection time. Labels were fixed to the freezing tubes in a manner that prevented the label from becoming detached after freezing.

All plasma samples were placed into a freezer at minus (–) 70°C or below within 1 hour after collection.

Sample Storage and Shipment
All plasma samples were to be stored frozen (at –70°C or below) until they were shipped to the analytical facility.

Analytical Methodology
The analysis of plasma samples was conducted by [redacted]. Validated analytical methods were used for the determination of concentration of oxymorphone from the plasma samples.

AE Monitoring
All AEs, including observed or volunteered problems, complaints, signs or symptoms, were recorded on the AE page of the CRF, regardless of whether associated with the use of EN3202. This included AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). To avoid colloquial expressions, the AE was to be recorded in standard medical terminology.

Throughout the study, all AEs were recorded in the subject CRF whether or not the event was considered treatment-related. This included any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness.

Conditions existing prior to the administration of the first dose were recorded as part of the subject's medical history. Any AE that was ongoing at completion/termination of the study was followed until resolution or up to 15 days. The investigator was to report serious adverse events (SAEs) via facsimile or telephone within 24 hours of first being advised of the AE. In the event discussion was necessary regarding treatment of the subject, the investigator was to contact the sponsor. The sponsor, in conjunction with the investigator, determined whether the AE had to be reported within 15 days to the FDA. If so, the sponsor reported the event to the FDA. The investigator was to transmit to the sponsor a written report of the circumstances and outcome within 3 days of reporting the SAE. The investigator was to report all SAEs to the IRB. The investigator was to evaluate each AE for duration, intensity, and relationship to (association with) study medication. The investigator was also to record the action taken, any treatment given, and the date and time of AE onset.

Precautions

Ethanol (ethyl ethanol) is absorbed rapidly and completely from the GI tract. After ingestion in the fasted state, peak blood levels are reached within 40 minutes. The presence of food in the gut delays the absorption. Over 90% of ethanol consumed is oxidized in the liver; the rest is excreted through the lungs and in the urine.

The central nervous system (CNS) is more markedly affected by acute ethanol consumption than any other organ system. Ethanol can lead to sedation and relief of anxiety, slurred speech, ataxia, impaired judgment, uninhibited behavior, or what is loosely called "drunkenness."

Ethanol is a vasodilator, probably as a result of both CNS effects and direct smooth muscle relaxation caused by the metabolite, acetaldehyde. In cases of severe intoxication, hypothermia consequent to vasodilation may be marked. The acute effects of ethanol on the stomach are related primarily to the toxic effect of ethanol on the mucosal membranes and have little to do with increased production of gastric acid. These include nausea, vomiting and acute gastritis. The most important goal in the treatment of acute ethanol intoxication is to prevent severe respiratory depression and aspiration of vomitus. The toxic dose of ethanol varies widely because of varying degrees of tolerance. A normal intolerant adult individual can metabolize 7 to 10 g of ethanol per hour (the ethanol content of 30 mL of 80 proof or 40% grain alcohol). Metabolic alterations may require treatment of hypoglycemia and ketosis by administration of glucose. Subjects who are dehydrated and vomiting should also receive electrolyte solutions to enhance the excretion of ketone bodies. If vomiting is severe, large amounts of potassium may also be required as long as renal function is normal.

Excessive oxymorphone effect may cause respiratory depression. This effect is antagonized by naloxone (Narcan®). For the present study, the clinical research facility had naloxone readily available in the event of respiratory depression. More than one injection of naloxone may have been necessary since the duration of action of oxymorphone may have exceeded that of the antagonist. Equipment to ventilate the subject in the event of an emergency was also available.

Additional information regarding AEs observed in other EN3202 clinical trials is outlined in the current Investigator's Brochure, which was provided to the Principal Investigator.

Subjects were administered naltrexone HCl to reduce the potential for opioid adverse effects. Naltrexone is a pure opiate antagonist with no opioid agonist properties. The most frequently observed adverse effects of naltrexone include abnormal liver function tests, nausea, difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, vomiting, low energy, joint and muscle pain, and headache. Additional information on naltrexone warnings and precautions can be obtained from the product prescribing information.

STATISTICAL METHODOLOGY

Pharmacokinetic and statistical analyses were performed [redacted]. All calculations, data presentations and analyses were performed using the SAS® System, Version 8.2 or later (SAS Institute, Cary, NC, USA).

Descriptive statistics, unless otherwise noted, include the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum value. Percentages were calculated using the number of subjects in the analysis population (i.e., pharmacokinetic or safety) for each treatment as the denominator. Unless stated otherwise, all summary tables present descriptive statistics and/or frequencies by treatment. All p-values and confidence intervals (CIs) reported are twotailed. All CIs are 90% intervals, unless otherwise noted, and all hypothesis testing was performed at α=0.05. All data collected on the CRFs or electronically transferred to PPD Data Management are presented in the data listings. In general, data presented in the listings are sorted by subject number, treatment (in the order received) and time point.

Determination of Sample Size

Twenty-eight subjects were to be enrolled in the study, with the expectation that at least 24 subjects would complete the study. This sample size is typical for bioavailability studies.

Analysis Populations

The pharmacokinetic population included all subjects with complete pharmacokinetic data during Treatment D and at least one other treatment (i.e., Treatment A, B or C). In addition, data from any subject who experienced emesis at any time during the labeled dosing interval (i.e., from 0 to 12 hours after receiving EN3202) within a treatment period were not included in the descriptive statistics or statistical analyses of the pharmacokinetic parameters. If there were a large number of subjects with emesis during this interval, additional statistical analyses and descriptive statistics were to be derived with these subjects included. The pharmacokinetic population was used for all pharmacokinetic summaries and analysis models. Any values that were excluded from the descriptive and inferential analysis are included in the subject data listings. This includes measurements from any excluded subjects, measurements from unscheduled collections, or extra measurements that may have arisen from two or more analyses of a plasma sample from the same time point.

The safety population for each treatment included all randomized subjects who received EN3202 for the period during which that treatment was administered. The safety population was used for all demographic and safety summaries. A table summarizing the number of subjects who were randomized, who were included in each analysis population, and who completed the study is provided. The number of subjects who did not complete the study and the reasons for discontinuation from the study are also presented. This table also includes the numbers of subjects included in the pharmacokinetic and safety populations for each treatment.

PK analysis

Calculation of Pharmacokinetic Parameters

Actual sampling times, rather than scheduled sampling times, were used in all computations of pharmacokinetic parameters. However, for ease of presentation, scheduled sampling times have been used to present results in summary tables and figures.

Missing plasma samples were treated as if they were not drawn. Plasma concentrations below the limit of quantification (BLQ) were set to zero in the computation of mean concentration values. Plasma concentrations that were BLQ prior to the first measurable concentrations were set to zero; plasma concentrations that were BLQ between measurable concentrations were treated as missing.

Plasma concentration data for oxymorphone and time deviation data for actual (versus scheduled) sample times are listed for each subject during each treatment. For each treatment, plasma concentration data were summarized over time using the following descriptive statistics: n, mean, SD, standard error (SE), coefficient of variation (CV [%]), median, minimum, maximum, and 25th and 75th percentiles.

Plots of mean (±SE) oxymorphone plasma concentrations over time (based on scheduled sampling time) for each treatment are provided in both linear and semi-logarithmic scales. Plots of plasma oxymorphone concentrations over time for each subject are also presented in both linear and semi-logarithmic scales. Any BLQ values that were between two non-BLQ values were excluded from the plots; other BLQ values were set to zero.

Analysis of Pharmacokinetic Results

The analysis of pharmacokinetic parameters focused on comparisons of EN3202 administered with ethanol solution (i.e., Treatments A, B, and C) to EN3202 administered with water (i.e., Treatment D). An analysis of variance (ANOVA) with fixed effects for sequence, period, and treatment and a random effect for subject nested within sequence, was performed on the natural logarithms of AUC0-t, AUC0-inf, and Cmax. The geometric mean ratios of each treatment (i.e., Treatments A, B, and C) compared to Treatment D for AUC0-t, AUC0-inf, and Cmax were calculated by exponentiating the mean difference of the log-transformed values. A 90% CI for each ratio (i.e., A: D, B:D, and C:D) was constructed by exponentiating the confidence limits for the logarithmic mean difference. In addition, the geometric least squares mean was computed for AUC0-t, AUC0-inf, and Cmax by exponentiating the least squares means from the ANOVA of the natural logarithm of these pharmacokinetic parameters. The

parameters .z and t½ were analyzed using similar methods but without log-transformation. For these two parameters, the least squares means and differences between the least square means (A-D, B-D, and C-D) were calculated.

For Tmax, the Hodges-Lehman method was used to calculate the point estimates and 95% CIs for the median of pairwise differences of interest (i.e., the median of the individual differences between each of Treatments A, B and C, and Treatment D).

Results

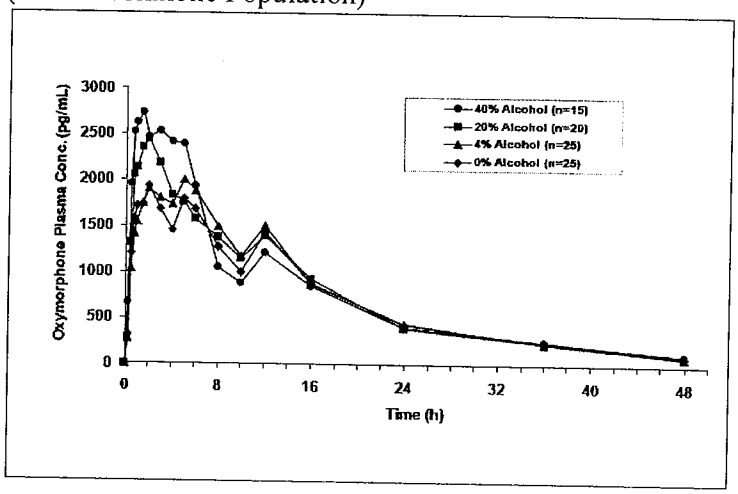
1. Discontinued Subjects

Subject Number	Randomized Treatment Sequence	Treatments Received	Reason for Discontinuation
111	BACD	B	Protocol violation
116	CBDA	C, B	Adverse event
122	CBDA	C	Withdrew consent
125	ADBC	A	Protocol violation
222	CBDA	C, B	Sponsor decision
Data Source: Appendix 16.4, Listings 1 and 10			
Treatment: A=EN3202 40 mg + 240 mL of 40% ethanol; B=EN3202 40 mg + 240 mL of 20% ethanol; C= EN3202 40 mg + 240 mL of 4% ethanol; D=EN3202 40 mg + 240 mL of water (0% ethanol).			

2. Descriptive Statistics for Demographic and Baseline Characteristics (All Subjects):

Characteristic	Statistic	All Subjects (n=30)
Age (years)	Mean (SD)	31.4 (7.1)
	Median	29
	Minimum – maximum	22 – 45
Gender	Male, n (%)	18 (60.0)
	Female, n (%)	12 (40.0)
Race	Caucasian, n (%)	16 (53.3)
	Black, n (%)	7 (23.3)
	Hispanic, n (%)	6 (20.0)
	Asian, n (%)	1 (3.3)
BMI (kg/m2)	Mean (SD)	27.7 (2.8)
	Median	28.6
	Minimum - maximum	21.6 – 32.6
Data Source: Appendix 16.2.2, Table 2		
BMI=body mass index; SD=standard deviation.		

3. Mean Oxymorphone Plasma Concentrations Versus Time by Treatment (Pharmacokinetic Population)



4. Pharmacokinetic Analyses

Descriptive Statistics for Oxymorphone Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)

		Treatment (Treatment Code)			
		EN3202 40 mg + 40% Ethanol (A)	EN3202 40 mg + 20% Ethanol (B)	EN3202 40 mg + 4% Ethanol (C)	EN3202 40 mg + Water (D)
Pharmacokinetic Parameter, unit	Statistic	(n=15)	(n=20)	(n=25)	(n=25)
AUC0-t, pg•h/mL	Mean (SD)	36385 (12441)	35389 (11495)	35146 (12534)	33350 (11864)
AUC0-inf, pg•h/mL	Mean (SD)	39973[a] (13595)	36889 (12356)	37551[b] (13452)	36034[b] (11388)
Cmax, pg/mL	Mean (SD)	3917 (1672)	3089 (1150)	2564 (1037)	2373 (870)
Tmax, h	Median (Min-max)	1.5 (0.75 – 6.00)	1.5 (0.75 – 8.00)	3.0 (1.00 – 12.00)	2.0 (0.50 – 12.00)
t½, h	Mean (SD)	11.3[a] (3.5)	9.9 (3.2)	10.4[b] (4.1)	10.7[b] (4.7)
[a]n=13					
[b]n=24					
max=maximum; min=minimum; SD=standard deviation.					

The analyses of AUC0-inf and AUC0-t showed that there was no main effect of treatment on these parameters (both $p>0.05$). The 90% CIs for the geometric mean ratios of the 20% ethanol treatment (B) to the 0% ethanol treatment (D) and the 4% ethanol treatment (C) to the 0% ethanol treatment (D) for both of these parameters included 1.0; lower 90% confidence limits ranged from 0.93 to 0.97, and upper 90% confidence limits ranged from 1.09 to 1.14.

Neither of the 90% CIs for the geometric mean ratios of the 40% ethanol treatment (A) to the 0% ethanol treatment (D) for the AUC parameters included 1.0; the 90% CIs were both 1.03 to 1.24.

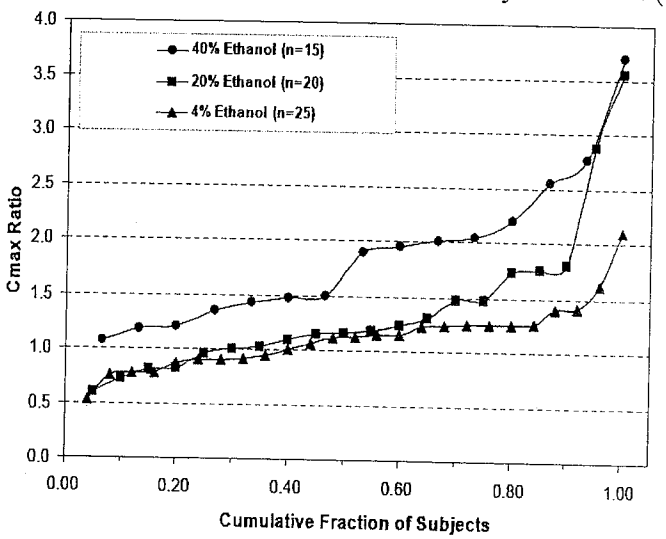
A statistically significant sequence effect (p=0.037) for AUC0-t was also noted. There was a statistically significant effect of treatment on Cmax (p<0.001). The geometric mean ratios showed that Cmax was 70%, 31%, and 7% higher for the 40% (A), 20% (B) and 4% (C) ethanol treatments, respectively, compared to the 0% ethanol treatment (D).

Neither of the 90% CIs for the geometric mean ratios of the 40% ethanol treatment (A) to the 0% ethanol treatment (D) (1.476, 1.966) and the 20% ethanol treatment (B) to the 0% ethanol treatment (D) (1.151, 1.488) included 1.0.

There was no statistically significant main effect of treatment on .z or on t½ (both p>0.05). For Tmax, the median differences between the 0% ethanol treatment (D) and each of the other three treatments ranged between 0.38 hr (Treatment C minus Treatment D) and – 1.56 hr (Treatment A minus Treatment D); all 95% CIs for these differences included zero.

Individual subject Cmax ratios for the 40% (A), 20% (B) and 4% (C) ethanol treatments, versus the 0% ethanol treatment (D) are plotted below. These ratios are shown as the cumulative fraction of subjects within a treatment. For example, for the 40% ethanol treatment (A), one-half of the subjects had a Cmax ratio below 1.5; 0.8 (80%) of the subjects had a Cmax ratio below 2.2. The Cmax ratio for the 40% ethanol treatment (A) was consistently higher than the other two ethanol treatments; however, there was a large degree of overlap between the ranges of Cmax ratios for each treatment. The 20% ethanol treatment (B) did not diverge from the 4% ethanol treatment (C) until a cumulative fraction of approximately 0.65, and a large divergence was only seen for the last two subject values (cumulative fraction above 0.92).

Cumulative Oxymorphone Cmax Ratios by Treatment (Pharmacokinetic Population)



Statistical Analyses of Oxymorphone Pharmacokinetic Parameters Excluding Tmax (Pharmacokinetic Population)

					Diff of	Ratio of	90% CI of			
				Geo.	LS Means	Geo. Means	the Ratio		P-Value	
Parameter	Trt	N	LS Meansb	Means	[-D]	[/D]	[/D]	Trt	Period	Seq
AUC[0-inf] (pg.hr/mL)	A	13	10.57	38763.92	0.12	**1.127**	(1.03, 1.24)	0.192	0.893	0.088
	B	20	10.46	34731.99	0.01	**1.010**	(0.93, 1.09)			
	C	24	10.47	35148.36	0.02	**1.022**	(0.95, 1.10)			
	D	24	10.45	34400.28						
AUC[0-t] (pg.hr/mL)	A	15	10.48	35710.93	0.12	1.129	(1.03, 1.24)	0.217	0.757	0.037
	B	20	10.40	32891.74	0.04	1.040	(0.95, 1.13)			
	C	25	10.42	33373.54	0.05	1.055	(0.97, 1.14)			
	D	25	10.36	31636.53						
Cmax (pg/mL)	A	15	8.243	3799.564	0.533	**1.703**	(1.476, 1.966)	<.001	0.742	0.114
	B	20	7.979	2918.795	0.269	**1.309**	(1.151, 1.488)			
	C	25	7.780	2393.368	0.070	**1.073**	(0.952, 1.209)			
	D	25	7.710	2230.474						
Lambda_z (1/hr)	A	13	0.06700		-0.00627			0.501	0.927	0.748
	B	20	0.07460		0.00133					
	C	24	0.07328		0.00001					
	D	24	0.07327							
T1/2 (hr)	A	13	11.49		0.76			0.699	0.778	0.268
	B	20	10.11		-0.62					
	C	24	10.48		-0.25					
	D	24	10.73							

*a*Treatment: A = EN3202 40 mg + 240 mL of 40% ethanol, B = EN3202 40 mg + 240 mL of 20% ethanol, C = EN3202 40 mg + 240 mL of 4% ethanol, D = EN3202 40 mg + 240 mL of water (0% ethanol).
*b*LS Means for AUC[0-t], AUC[0-inf] and Cmax are on the logarithm scale. LS means for Lambda_z and T1/2 are on the original scale.
ANOVA=analysis of variance; CI=confidence interval; Diff=difference; Geo=geometric; LS=least squares; Seq=sequence; Trt=treatment.
Note: An ANOVA model was performed on Lambda_z, T1/2 and the natural logarithms of AUC[0-t], AUC[0-inf] and Cmax. The model included sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect. Point estimates and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

Statistical Analysis of Oxymorphone Tmax (Pharmacokinetic Population)

Parameter	Treatment Comparisona	N	Median Difference	95% CI for Median Difference
Tmax (hr)	A - D	15	-1.56	(-3.12, 0.25)
	B - D	20	-0.75	(-2.15, 0.35)
	C - D	25	0.38	(-0.25, 1.25)

*a*Treatment: A = EN3202 40 mg + 240 mL of 40% ethanol, B = EN3202 40 mg + 240 mL of 20% ethanol, C = N3202 40 mg + 240 mL of 4% ethanol, D = EN3202 40 mg + 240 mL of water (0% ethanol).
CI=confidence interval.
Note: Hodge Lehmann method was performed to calculate the point estimates, and 95% CI for the median pair-wise differences of Tmax between each treatment (A, B, and C) and Treatment D.

A similar pattern of results was seen when subjects with emesis were included in the statistical analyses of the pharmacokinetic parameters. A statistically significant main effect of treatment on Cmax was seen ($p<0.001$), and the mean Cmax values increased as the ethanol percentage of the treatment increased. The geometric mean ratios showed that Cmax was 62%, 15%, and 7% higher for the 40% (A), 20% (B) and 4% (C) ethanol treatments, respectively, compared to the 0% ethanol treatment (D).

The 90% CI for the geometric mean ratio of Treatments the 40% ethanol treatment (A) to the 0% ethanol treatment (D) (1.365, 1.931) did not include 1. No statistically significant differences between treatments were seen for any other pharmacokinetic parameters.

5. Safety Information

Study Treatments Received by Subjects who discontinued from the Study

Subject Number	Study Treatment(s) (Treatment Code) Received in Order of Receipt
111	EN3202 40 mg + 240 mL 20% ethanol solution (B)
116a	EN3202 40 mg + 240 mL 4% ethanol solution (C); EN3202 40 mg + 20% ethanol solution (B)
122b	EN3202 40 mg + 240 mL 4% ethanol solution (C)
125	EN3202 40 mg + 240 mL 40% ethanol solution (A)
222c	EN3202 40 mg + 240 mL 4% ethanol solution (C); EN3202 40 mg + 20% ethanol solution (B)

*a*Subject received naltrexone on Day -1 during Treatment Period 3, but was discontinued before receiving naltrexone on Day 1 (-2 hr) or Treatment Period 3 study medication.
*b*Subject was discontinued before receiving naltrexone 12 hours after dosing with study medication during Treatment Period 1.
*c*Subject received naltrexone on Day -1 and on Day 1 (-2 hr) during Treatment Period 3, but was discontinued before receiving Treatment Period 3 study medication.
Note: Subjects received all planned treatments during a treatment period (i.e., Day -1 naltrexone, Day 1 [-2 hr] naltrexone, study medication, and Day 1 [+12 hr] naltrexone) unless otherwise noted.

Treatment-Emergent Adverse Events

The percentages of subjects reporting one or more TEAEs were highest during treatment with the 40% and 20% ethanol solutions (14 of 26 subjects [54%] during Treatment A and 12 of 28 subjects [43%] during Treatment B). Percentages of subjects reporting one or more TEAEs during the remaining two treatments were lower and similar to each other

(6 of 28 subjects [21%] during Treatment C and 5 of 25 subjects [20%] during Treatment D).

Adverse Events by System Organ Class
The most frequently occurring TEAEs were in the GI and nervous system disorders system organ classes. The occurrence of GI disorders was higher during treatment with the 40% and 20% ethanol solutions: 12 of 26 subjects (46%) during Treatment A and 6 of 28 subjects (21%) during Treatment B, compared with 3 of 28 subjects (11%) during Treatment C and 3 of 25 subjects (12%) during Treatment D. Nervous system disorders occurred more frequently during Treatment B (7 of 28 subjects [25%]) than during other treatments (4 of 26 subjects [15%] during Treatment A, 4 of 28 subjects [14%] during Treatment C and 2 of 25 subjects [8%] during Treatment D).

Adverse Events by Preferred Term
Vomiting was the most frequently occurring TEAE, and its incidence increased as the ethanol solution percentage increased. Ten of 26 subjects (39%) reported vomiting during Treatment A, compared with 6 of 28 subjects (21%) during Treatment B, and 1 of 28 subjects (4%) during Treatment C. No subject reported vomiting during Treatment D.

Other frequently occurring TEAEs included headache, nausea and dizziness. Headache was reported by 4 of 26 subjects (15%) during Treatment A, 4 of 28 subjects (14%) during Treatment B, 3 of 28 subjects (11%) during Treatment C and 2 of 25 subjects (8%) during Treatment D.

Nausea was reported by 4 of 26 subjects during Treatment A (15%), 1 of 28 subjects (4%) during Treatment C and 1 of 25 subjects (4%) during Treatment D; no subject reported nausea during Treatment B. Dizziness was reported by 3 of 28 subjects (11%) during Treatment B, 2 of 28 subjects (7%) during Treatment C, and 1 of 26 subjects (4%) during Treatment A; no subject reported dizziness during Treatment D. All other TEAEs occurred in 2 or fewer subjects during each treatment.

There were no TEAEs that were considered severe in intensity by the investigator. With the exception of vomiting, the large majority of TEAEs were considered mild in intensity. All occurrences of vomiting were considered moderate in intensity.

Vomiting
Headache
Nausea
Dizziness

Incidence Rates for All Treatment-Emergent Adverse Events by Treatment, System Organ Class and Preferred Term (Safety Population) (Page 1 of 2)

System Organ Class/ Preferred Term	Treatment A (N=26)	Treatment B (N=28)	Treatment C (N=28)	Treatment D (N=25)	Overall (N=30)
Number of Subjects With at Least One Treatment Emergent Adverse Event	14 (53.8%)	12 (42.9%)	6 (21.4%)	5 (20.0%)	21 (70.0%)
Gastrointestinal disorders	12 (46.2%)	6 (21.4%)	3 (10.7%)	3 (12.0%)	18 (60.0%)
Vomiting	10 (38.5%)	6 (21.4%)	1 (3.6%)	0	15 (50.0%)
Nausea	4 (15.4%)	0	1 (3.6%)	1 (4.0%)	5 (16.7%)
Abdominal pain	1 (3.8%)	0	0	1 (4.0%)	2 (6.7%)
Dry mouth	0	0	1 (3.6%)	1 (4.0%)	2 (6.7%)
Diarrhoea	0	1 (3.6%)	0	0	1 (3.3%)
Nervous system disorders	4 (15.4%)	7 (25.0%)	4 (14.3%)	2 (8.0%)	10 (33.3%)
Headache	4 (15.4%)	4 (14.3%)	3 (10.7%)	2 (8.0%)	9 (30.0%)
Dizziness	1 (3.8%)	3 (10.7%)	2 (7.1%)	0	4 (13.3%)
Burning sensation	0	1 (3.6%)	0	0	1 (3.3%)
Sinus headache	0	1 (3.6%)	0	0	1 (3.3%)
Somnolence	0	1 (3.6%)	0	0	1 (3.3%)
Tremor	0	1 (3.6%)	0	0	1 (3.3%)
General disorders and administration site conditions	3 (11.5%)	2 (7.1%)	1 (3.6%)	0	4 (13.3%)
Asthenia	1 (3.8%)	1 (3.6%)	0	0	2 (6.7%)
Feeling drunk	2 (7.7%)	0	0	0	2 (6.7%)
Feeling hot	0	1 (3.6%)	1 (3.6%)	0	1 (3.3%)
Respiratory, thoracic and mediastinal disorders	1 (3.8%)	2 (7.1%)	0	1 (4.0%)	3 (10.0%)
Pharyngolaryngeal pain	1 (3.8%)	2 (7.1%)	0	0	3 (10.0%)
Pharyngeal hypoaesthesia	0	0	0	1 (4.0%)	1 (3.3%)

System Organ Class/ Preferred Term	Treatment A (N=26)	Treatment B (N=28)	Treatment C (N=28)	Treatment D (N=25)	Overall (N=30)
Skin and subcutaneous tissue disorders	1 (3.8%)	2 (7.1%)	0	0	3 (10.0%)
Dermatitis contact	1 (3.8%)	0	0	0	1 (3.3%)
Hyperhidrosis	0	1 (3.6%)	0	0	1 (3.3%)
Pruritus generalised	0	1 (3.6%)	0	0	1 (3.3%)
Rash macular	0	1 (3.6%)	0	0	1 (3.3%)
Metabolism and nutrition disorders	1 (3.8%)	0	0	0	1 (3.3%)
Dehydration	1 (3.8%)	0	0	0	1 (3.3%)
Musculoskeletal and connective tissue disorders	0	1 (3.6%)	0	0	1 (3.3%)
Back pain	0	1 (3.6%)	0	0	1 (3.3%)
Psychiatric disorders	0	1 (3.6%)	1 (3.6%)	0	1 (3.3%)
Bruxism	0	1 (3.6%)	1 (3.6%)	0	1 (3.3%)
Disorientation	0	1 (3.6%)	0	0	1 (3.3%)

Treatment-Related, Treatment-Emergent Adverse Events

The percentages of subjects reporting one or more treatment-related TEAEs were highest during treatment with the 40% and 20% ethanol solutions (9 of 26 subjects [35%] during Treatment A and 8 of 28 subjects [29%] during Treatment B). Percentages of subjects reporting one or more treatment-related TEAEs during the remaining two treatments were lower and similar to each other (5 of 28 subjects [18%] during Treatment C and 4 of 25 subjects [16%] during Treatment D).

With the exception of vomiting, the majority of frequently occurring TEAEs (i.e., headache, nausea and dizziness) were considered related to treatment with EN3202. The majority of occurrences of vomiting during Treatment A and some of those occurring during Treatment B were considered not related to EN3202 treatment.

DISCUSSION AND OVERALL CONCLUSIONS

Pharmacokinetics

The results of this study demonstrated that with graded concentrations of ethanol, there was no evidence of disintegration or dose dumping; but, there was evidence of a "dose response" for the peak average oxymorphone plasma concentration.

Increases in peak average oxymorphone plasma concentrations (Cmax) of 70%, 31%, and 7% were noted with co-administration of 240 mL 40% ethanol, 20% ethanol and 4% ethanol treatments, respectively, compared to the 0% ethanol treatment.

Some subjects demonstrated higher peak concentrations, up to 3.7 times higher, with 40% ethanol than in the absence of ethanol. The analyses of AUC0-inf and AUC0-t showed that there was no effect of treatment on these parameters (both $p>0.05$). For the geometric mean ratios of 40% ethanol, 20% ethanol and 4% ethanol to 0% ethanol for AUC0-inf and AUC0-t, the 90% CIs ranged from 0.93 to 1.24.

A similar pattern of results was seen when subjects with emesis within 12 hours of EN3202 dosing were included in the analyses.

In vitro data show that 40% ethanol does not increase the dissolution rate of the EN3202 40 mg tablet.

However, data from the present study demonstrate that co-administration of 240 mL of 40% ethanol, and to a lesser extent 20% ethanol, increased the Cmax of oxymorphone from the 40 mg tablet while having no demonstrable effect on the AUC. The results suggests that ethanol does not directly affect the formulation, i.e., does not cause the formulation to disintegrate more quickly, but has another effect(s) that can lead to an apparent increased rate of absorption of oxymorphone.

Safety

There were no serious or unexpected AEs in this study. One subject was discontinued from the study due to AEs (generalized pruritus, generalized macular rash and burning sensation). These events occurred approximately 1 hour after receiving naltrexone on Day –1 of Treatment Period 3 and were considered unrelated to EN3202. There were no severe AEs. The most frequently occurring AE was vomiting, which occurred more frequently during treatment with higher ethanol solution percentages. The majority of occurrences of vomiting were considered moderate in intensity by the investigator. Other AEs that occurred in more than two subjects during a particular treatment included headache, nausea and dizziness. The majority of these events were considered mild in intensity by the investigator. Increases from baseline in mean heart rate were seen 6 hours after dosing with all four treatments. The magnitude of these mean increases from baseline increased with the ethanol solution percentage. This pattern was less apparent 12 hours after dosing, and was not seen 24 hours after dosing. Sporadic abnormalities in

clinical laboratory tests were seen, but there was no pattern to their occurrence and none of the abnormalities was clinically significant.

The results of this study indicate that there is an interaction between ethanol and EN3202 when the two are co-administered. This interaction is manifested as an ethanol dose-related increase in peak EN3202 plasma concentrations (Cmax). There was no effect on AUC.

4.3 Consult Review (including Pharmacometric Reviews) – Not Applicable

4.4 Cover Sheet and OCPB Filing/Review Form – Not Applicable

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/s/

David Lee
6/16/2006 02:44:57 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/16/2006 02:58:44 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

IR oxymorphone tablet labeling review

NDA: 21-610 21-611	Submission Date: 12/19/02 12/20/02
Submission Type; Code:	505 (b) (1); 1S
Brand/Code Name:	To-be-determined
Generic Name:	Oxymorphone Hydrochloride
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCPB Division:	DPE 2
ORM Division:	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor:	Endo Pharmaceuticals Inc.
Relevant IND(s):	58,602; 56,919
Relevant NDA(s):	11-707; 11-738
Formulation; Strength(s):	5, 10 mg IR 5, 10, 20, 40 mg ER
Proposed Indication:	Management of moderate to severe pain where the use of an opioid is appropriate
Proposed Dosage Regimen:	This is contraindicated in patients with severe hepatic impairment. The dose should be titrated (initiate with IR every 6 — hours as needed and maintain pain management with ER bid) based upon the individual patient's response and condition (e.g., opioid-naïve patients should be started on 5 mg IR every 6 — hours as needed.)

The following edits to the package inserts are proposed for the oxymorphone IR oxymorphone tablet. Where appropriate, the Applicant's proposed package insert was edited with ~~strikeouts~~, deletes and additions. Reviewer Comments are *italicized* and **bolded** when needed throughout the document.

7 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

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

/s/

David Lee
10/15/03 03:43:56 PM
BIOPHARMACEUTICS

As a formality, a labeling review is formulated and submitted into DFS.

Suresh Doddapaneni
10/16/03 08:22:58 AM
BIOPHARMACEUTICS

1ST Cycle

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-610	Submission Date: 12/19/02
21-611	12/20/02
Submission Type; Code:	505 (b) (1); 1S
Brand/Code Name:	To-be-determined
Generic Name:	Oxymorphone Hydrochloride
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCPB Division:	DPE 2
ORM Division:	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor:	Endo Pharmaceuticals Inc.
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1 Executive Summary

Endo Pharmaceuticals Inc. has submitted two original NDAs, N21-610 (ER formulation) and N21-611 (IR formulation) for approval of oxymorphone tablets in patients who need management of moderate to severe pa in. Currently, oxymorphone hydrochloride IR tablets are not marketed in any countries. However, IR tablets (i.e., 2 mg, 5 mg, and 10 mg) were marketed by Endo under the Trade Name Numorphan® Tablets from 1959 (N 11-737) until 1979, and the NDA for this product was officially withdrawn in 1979 due to lack of marketing interest. Oxymorphone is currently marketed by Endo as parenteral (N 11-707) and rectal suppository (N 11-738) formulations.

The Applicant submitted 14 analytical and 16 clinical pharmacology reports, respectively for review. After reviewing all studies, it is felt that study reports submitted by the Applicant are adequate and the information presented within are adequate and sufficient in order to describe the characteristics of oxymorphone tablets. No further studies are necessary.

Oxymorphone IR and ER tablets exhibited dose proportionality (tested up to 40 mg) with both single and multiple doses. No accumulation was observed after multiple administrations for both IR (qid) and ER (bid) tablets. In general, steady-state conditions were achieved within 3 to 4 days post dosing. The extent of absorption (AUC) was comparable between IR and ER tablets. However, the rate of absorption (Cmax) was higher (approximately 35%) for IR tablets, compared with ER tablets, which is an expected phenomenon, due to the nature of the drug delivery system.

With respect to food effect, oxymorphone IR tablets exhibited 38% increase in both AUC and Cmax with food intake. ER tablets exhibited 51-58% increase in Cmax with food intake. A little to no AUC change was observed for ER tablets. In the clinical trials oxymorphone ER was administered with or without food.

Coadministration of naltrexone with oxymorphone did not alter oxymorphone's disposition. *In vitro* studies in human recombinant human liver microsomes and hepatocyte indicated that oxymorphone does not inhibit the activity of CYP450 1A2, 2C19, 2D6, or 2E1. However, there is a hint of 2C9 and 3A4 inhibition (inhibitory concentration was 300- to 1000- fold and 10,000-fold higher, respectively, than the expected clinical concentration). Currently, two in vivo drug interaction studies are ongoing to investigate the effects of CYP450 2C9 and 3A4.

The single dose (20 mg ER tablet) plasma oxymorphone concentrations were approximately 36 and 45% higher in AUC and Cmax, respectively, for elderly subjects than in young subjects. Likewise, after multiple doses, plasma oxymorphone concentrations were approximately 40 and 34 % higher in AUC and Cmax, respectively, for elderly subjects. Specifically, the mean oxymorphone AUC in elderly females were greater than in elderly males by approximately 26%; and the AUC in young females were greater than in young males by approximately 24%. Titration of dose needs to be undertaken with caution in the elderly.

The single dose (20 mg ER tablet) plasma oxymorphone concentrations were 19 and 43 % higher in AUC and Cmax, respectively, for women. Likewise, after multiple doses, plasma oxymorphone concentrations were 14 and 20% higher in AUC and Cmax, respectively for women.

After a single dose 20 mg ER tablet, renal impairment was associated with an increase in plasma oxymorphone AUC and a reduction in renal excretion of oxymorphone and its' major metabolite oxymorphone-3-glucuronide. Mean oxymorphone AUC was increased by 25, 57 and 65 % in mild, moderate, and severe renal impaired subjects, respectively.

There was no change in t1/2 of oxymorphone among all three groups. Titration of dose needs to be undertaken cautiously in patients with moderate and severe renal impairment.

After a single dose 20 mg ER tablet, individuals with moderate or severe liver disease had clinically significant increases in plasma oxymorphone concentrations (AUC was increased up to 3.7-(mean value) and 12.2-fold (one patient) in moderate and severe liver disease subjects, respectively). Titration of dose needs to be undertaken with extreme caution in moderately impaired subjects. Oxymorphone should be contraindicated in severely impaired subjects. However, individuals with mild liver disease did not appear to have a significant increase (approx. 1.5 fold increase). There was no change in t1/2 of oxymorphone among all three groups. It is noted that the Applicant previously proposed contraindication for the severe hepatic impairment (I 56919 serial # 146; submission date 5/23/02).

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed the original NDAs 21-610 and 21-611.

From OCPB point of view, the information contained in the NDA is acceptable. No further information is needed at this time.

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Team Leader, DPE2/OCPB

2 Table of Contents

3 Summary of CPB Findings

1. The presence of multiple peaks was observed after single- and multiple administration of oxymorphone, suggesting the presence of enterohepatic recycling. This finding is a known phenomenon in opioids. Due to the similarity in primary structure between oxymorphone and morphine, biliary excretion can be expected to be a significant route of excretion of oxymorphone and its metabolites.
2. Oxymorphone's plasma protein binding is 10 – 12 % .
3. The mean absolute bioavailability was 10.8% for IR tablet.
4. Oxymorphone is extensively metabolized and < 1 % of the administered dose is excreted unchanged in the urine. Oxymorphone is metabolized by reduction of the 6-keto group to 6-OH-oxymorphone, and further metabolized to oxymorphone-3-glucuronide, a major metabolite.
5. After a single 1 x 40 mg ER tablet administration, the mean oxymorphone Cmax in the fed state (4.25 ng/mL) was about 52% higher than the Cmax in the fasted state (2.79 ng/mL). No AUC increase was observed.
6. After a single 4 x 10 mg IR tablets administration, both the mean oxymorphone AUC and Cmax were increased by approximately 38% after a high fat meal.
7. After a single dose IR tablet oxymorphone PK parameters (Mean (SD)) are;

Variable	5 mg	10 mg	20 mg
AUC (ng•hr/mL)	4.48 (2.07)	9.10 (3.40)	20.07 (5.80)
AUCT (ng•hr/mL)	2.77 (1.40)	6.76 (3.18)	17.67 (5.76)
AUC0-6 (ng•hr/mL)	2.11 (1.00)	4.28 (1.49)	9.29 (3.04)
Cmax (ng/mL)	1.10 (0.55)	1.93 (0.75)	4.39 (1.72)
Tmax (hr)*a*	0.50 (0.25-1.00)	0.50 (0.25-1.50)	0.50 (0.25-1.00)
CL/F (L/min)	23.53 (13.18)	21.42 (9.92)	18.21 (6.16)
t½ (hr)	7.25 (4.40)	7.78 (3.58)	9.43 (3.36)

a: median

8. After multiple administration of IR tablets, oxymorphone PK parameters (Mean (SD)) are;

Variable	5 mg q 6 hr	10 mg q 6 hr	20 mg q 6 hr
AUCss (ng•hr/mL)	4.63 (1.49)	10.19 (3.34)	21.10 (7.59)
Cmax (ng/mL)	1.73 (0.62)	3.51 (0.91)	7.33 (2.93)
Cmin (ng/mL)	0.49 (0.17)	1.16 (0.43)	2.47 (0.94)
Tmax (hr)*a*	0.50 (0.25-6.00)	0.50 (0.25-1.00)	0.50 (0.25-1.50)
Cavg (ng/mL)	0.77 (0.25)	1.70 (0.56)	3.52 (1.27)
CL/F (L/min)	19.23 (4.27)	17.63 (4.42)	17.68 (6.14)

a: median

9. After a single dose ER tablet, oxymorphone PK parameters (Mean (SD)) are;

Variable	5 mg	10 mg	20 mg	40 mg
AUCT (ng•hr/mL)	2.13 (1.28)	6.66 (3.55)	15.08 (6.95)	35.37 (16.19)
AUC (ng•hr/mL)	4.54 (2.04)	8.94 (4.16)	17.80 (7.22)	37.90 (16.20)
AUC_{0-12} (ng•hr/mL)	1.74 (0.94)	4.44 (1.70)	8.50 (4.04)	18.47 (9.98)
Cmax (ng/mL)	0.27 (0.13)	0.65 (0.29)	1.21 (0.77)	2.59 (1.65)
Tmax (hr)[a]	3.00 (1.00–12.00)	3.00 (0.50–6.00)	4.00 (1.00–12.00)	2.50 (0.50–12.00)
CL/F (L/min.)	26.36 (25.21)	22.26 (9.27)	20.93 (6.46)	19.44 (5.06)
t½ (hr)	11.30 (10.81)	9.83 (5.68)	9.89 (3.21)	9.35 (2.94)

a: median

10. After multiple ER tablet administration: oxymorphone PK parameters (Mean (SD)) are;

Variable	5 mg q 12 hr	10 mg q 12 hr	20 mg q 12 hr	40 mg q 12 hr
AUCss (ng•hr/mL)	5.60 (3.87)	9.77 (3.52)	19.28 (8.32)	36.98 (13.53)
Cmax (ng/mL)	0.70 (0.55)	1.24 (0.56)	2.54 (1.35)	4.47 (1.91)
Tmax (hr)[a]	1.50 (0.50–12.00)	2.00 (0.50–12.00)	1.25 (0.50–6.00)	3.50 (0.50–10.00)
CL/F (L/min.)	18.18 (6.31)	19.33 (7.29)	20.23 (7.96)	19.76 (5.57)
Cmin (ng/mL)	0.41 (0.59)	0.64 (0.26)	1.22 (0.52)	2.33 (1.16)
Cavg (ng/mL)	0.47 (0.32)	0.81 (0.29)	1.61 (0.69)	3.08 (1.13)

a: median

11. After single- and multiple-dosing, the oxymorphone pharmacokinetic parameters were dose proportional (#7-10).
12. Comparison of exposure (AUC) from a same strength IR and ER tablets (20 mg) after single and multiple doses exhibited similar AUC values.
13. The single-dose and steady-state plasma concentrations of oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide were higher in elderly subjects (≥65 years of age) than in young subjects (20 to 40 years of age).
14. The mean oxymorphone AUC in elderly females were greater than in elderly males by approximately 26%; and the AUC in young females were greater than in young males by approximately 24%.
15. After a single dose 20 mg ER tablet, individuals with moderate or severe liver disease had clinically significant increases in plasma oxymorphone concentrations (AUC was increased up to 3.7-(mean value) and 12.2-fold (one patient) in moderate and severe liver disease subjects). Titration of dose needs to be undertaken with extreme caution in moderately impaired subjects. Oxymorphone should be contraindicated in severely impaired subjects. Individuals with mild liver disease did not appear to have a significant increase (approx. 1.5 fold increase). There was no change in t1/2 of oxymorphone among all three groups.
16. After a single dose 20 mg ER tablet, renal impairment was associated with an increase in plasma oxymorphone AUC and a reduction in renal excretion of both oxymorphone and oxymorphone-3-glucuronide, a major metabolite. Mean oxymorphone AUC was increased by 25, 57 and 65 % in mild, moderate, and severe renal impaired subjects, respectively. There was no change in t1/2 of oxymorphone among all three groups. Titration of dose needs to be undertaken cautiously in subjects with moderate and severe renal impairment.

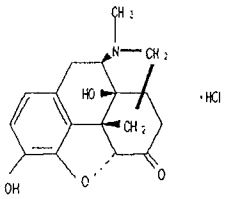
17. Coadministration of naltrexone with oxymorphone did not alter oxymorphone's disposition. *In vitro* studies in human recombinant human liver microsomes and hepatocyte indicated that oxymorphone does not inhibit the activity of CYP450 1A2, 2C19, 2D6, or 2E1. Currently, two clinical drug interaction studies are ongoing to investigate the effects of CYP450 2C9 and 3A4.
18. To-be-marketed formulation for both IR and ER tablets are bioequivalent to clinical trial tablet formulations.
19. In vitro-in vivo correlation was observed for ER tablets.
20. There is no exposure-response relationship information for IR tablets. The Applicant stated that they did not observe any exposure-response relationship for ER tablets. However, additional analysis exhibited there seems to be a trend of decreasing pain intensity when oxymorphone concentration increases. However, this needs to be further confirmed.

4 QBR

4.1 General Clinical Pharmacology

What is the pharmacological class for oxymorphone?

Oxymorphone (14-hydroxydihydromorphinone) is a semisynthetic opioid agonist, derived from thebaine, that modulates pain by acting with significant specificity at the mu opioid receptor site.



4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride

Oxymorphone has a significantly higher parenteral analgesic potency compared to parenteral morphine. The structure of oxymorphone is related to morphine, differing in a ketone group substitution at the C-6 position of morphine and saturation of the 7-8 double-bond. The ketone group substitution is stated to make the molecule more lipid soluble, leading to rapid access into the brain and spinal cord through penetration of neurovascular membranes.

What is oxymorphone's protein binding information?

Protein binding of oxymorphone is low; binding of ^{3}H-oxymorphone ranged from [redacted]

Are metabolites active?

Oxymorphone is rapidly absorbed following oral administration and is subject to extensive first-pass metabolism (<1% of the administered dose is excreted unchanged in the urine).

Oxymorphone is initially metabolized, by reduction of the 6-keto group, to 6-OH-oxymorphone. 6-OH-oxymorphone appears to be roughly equi-potent to oxymorphone in animal analgesic assays. In healthy subjects, the mean plasma 6-OH-oxymorphone AUC is approximately 50-70% of the oxymorphone AUC following single oral doses but is essentially equivalent to the parent compound at steady-state. On average, 0.25% to 0.62% of the dose was excreted in the urine as 6-OH-oxymorphone in subjects with normal hepatic and renal function. This percentage increased to 2.4% when the urine was pre-treated with glucuronidase, indicating that the urine contains glucuronide conjugates of 6-OH-oxymorphone.

The primary metabolite found in plasma and urine is oxymorphone-3-glucuronide, and appears to be non-active. On a molar basis, the mean plasma AUC for oxymorphone-3-glucuronide is approximately 90- fold higher than the parent compound. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide (in the absence of hepatic or renal dysfunction). Although other glucuronide conjugates of oxymorphone may be present, these compounds do not appear to represent a significant proportion of the drug excreted in the urine.

What is the oral bioavailability of IR tablet (and solution)?

After a single dose of 10 mg IR tablet and 10 mg oral solution (10 mL prepared from 10 x 1 mg/mL i.v. injection), the mean absolute oral bioavailability (F%) was 10.8% and 10.2% for the IR tablet and oral solution, respectively.

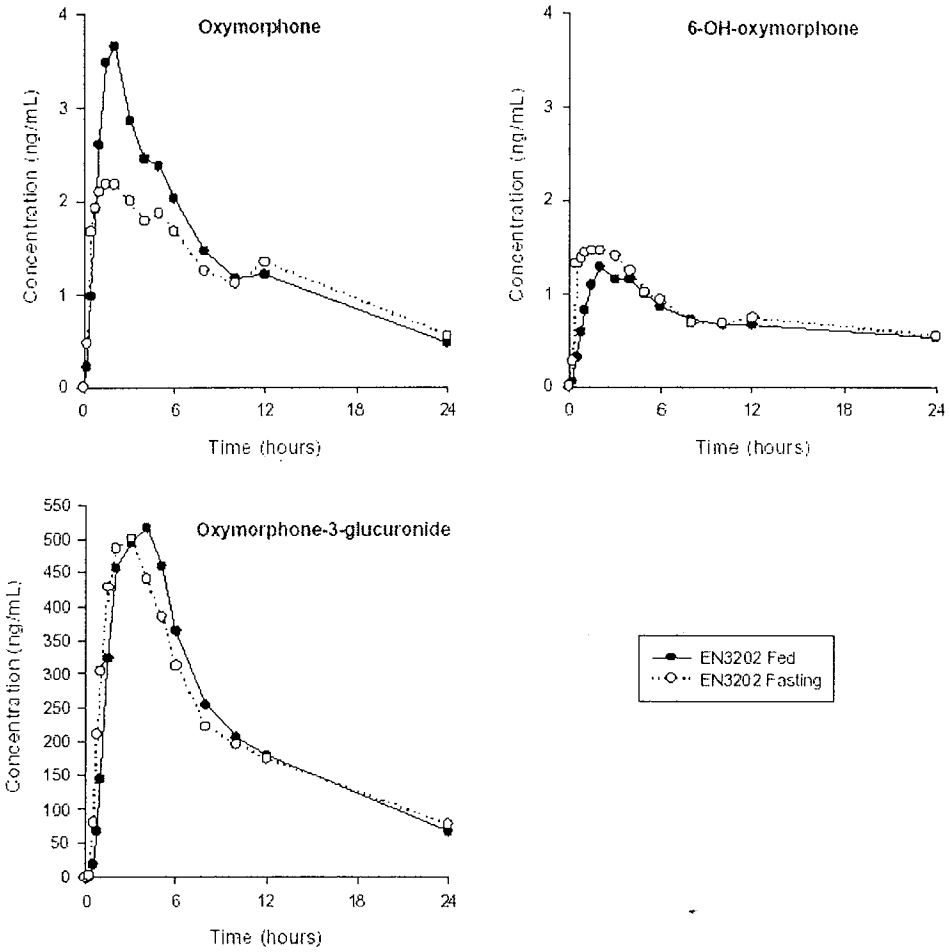
Is there a food effect?

After a single dose of 1 x 40 mg ER and 4 × 10 mg IR tablets under fed and fasted conditions (Study EN3202-008), in general, tablets with a high fat meal was associated with higher average plasma oxymorphone concentrations until approximately 8 hours after dose administration. There was no evidence of dose dumping.

ER tablets

Specifically, for 1 x 40 mg ER, the mean oxymorphone Cmax in the fed state (4.25 ng/mL) was about 52% higher than the Cmax in the fasted state (2.79 ng/mL). No AUC increase was observed in fed state.

Figure - Mean Plasma Concentrations Following 40 mg ER (1 x 40 mg) tablets under fed and fasting conditions:



IR tablets

Both the mean oxymorphone AUC and Cmax were increased by approximately 38% when 4 x 10 mg IR tablets were administered after a high fat meal.

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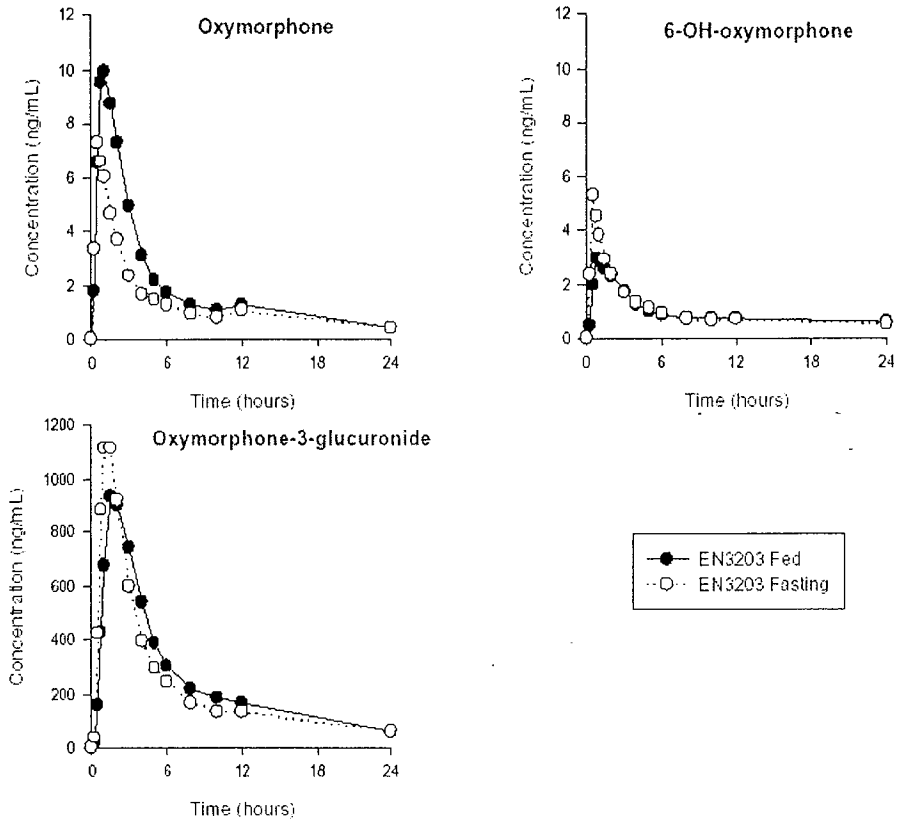
Figure - Mean plasma conc. after a single 4 x 10 mg IR tablets under fed / fasting conditions:



How are two different formulations produced by different manufacturing sites compare with each other ? Are the clinical and To-be-Marketed formulations bioequivalent?

IR tablets

Oxymorphone IR tablets were initially manufactured by [redacted]. The Applicant subsequently decided to change the site of manufacture to Novartis Consumer Health (NCH or Novartis) for later clinical trials and for the commercial product. There were two studies

After a 10 mg IR single dose crossover study, IR tablets manufactured by NCH are bioequivalent to those manufactured by [redacted]:

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Analyte/Parameter	(Test) NCH (1 × 10 mg)	(Reference) [redacted] (1 × 10 mg)	Ratio[a]	90% Confidence Interval Lower	Upper
Oxymorphone					
ln-AUC	7.4836	7.3449	1.0189	0.9350	1.1103
ln-AUCT	6.0672	5.9215	1.0246	0.9227	1.1378
ln-C_{max}	1.8930	1.7792	1.0640	0.9507	1.1908
6-OH-oxymorphone					
ln-AUC	7.6122	7.3942	1.0295	0.9212	1.1505
ln-AUCT	5.6578	5.5004	1.0286	0.9226	1.1469
ln-C_{max}	1.3605	1.2792	1.0636	0.9763	1.1587
Oxymorphone-3-glucuronide					
ln-AUC	1282.86	1300.43	0.9865	0.9624	1.0112
ln-AUCT	1193.22	1214.06	0.9828	0.9536	1.0129
ln-C_{max}	257.404	250.794	1.0264	0.9823	1.0724

[a]Exponent (ln-test – ln-reference)

ER Tablets

After a 40 mg ER single dose crossover study, ER tablets manufactured by NCH are bioequivalent to those manufactured by [redacted].

Table - Comparison of Geometric LS Means, Ratio, and 90% Confidence Interval of Plasma Pharmacokinetic Results:

Analyte/Parameter Oxymorphone-	Test Novartis (1×40 mg)	Reference [redacted] (1×40 mg)	Ratio	90% C. I. Range Lower–Upper
ln-AUC (ng•hr/mL)	37.1	36.5	1.02	0.96–1.08
ln-AUCT (ng•hr/mL)	33.7	33.6	1.01	0.94–1.08
ln-Cmax (ng/mL)	2.4	2.4	0.97	0.89–1.04

C. I. = confidence interval

Does oxymorphone IR (5, 10, 20 mg doses) and ER tablets show linearity / dose-proportionality?

IR Tablets

After a single dose of 5, 10 and 20 mg (2 x 10 mg) IR tablets, the data indicated that dose proportionality was achieved, however, for 20 mg IR tablet, the dose-normalized AUC was slightly greater than that of the other two doses:

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Table - PK parameters after single doses:

Variable	5 mg	10 mg	20 mg
OXM			
AUC (ng•hr/mL)	4.48 (2.07)	9.10 (3.40)	20.07 (5.80)
AUCT (ng•hr/mL)	2.77 (1.40)	6.76 (3.18)	17.67 (5.76)
AUC_{0-6} (ng•hr/mL)	2.11 (1.00)	4.28 (1.49)	9.29 (3.04)
Cmax (ng/mL)	1.10 (0.55)	1.93 (0.75)	4.39 (1.72)
Tmax (hr)a	0.50 (0.25-1.00)	0.50 (0.25-1.50)	0.50 (0.25-1.00)
CL/F (L/min)	23.53 (13.18)	21.42 (9.92)	18.21 (6.16)
$\lambda Lamda_z$ (hr^{-1})	0.1534 (0.1308)	0.1257 (0.0997)	0.0835 (0.0331)
t½ (hr)	7.25 (4.40)	7.78 (3.58)	9.43 (3.36)
a : median			
6-OH-OXM			
AUC (ng•hr/mL)	4.02 (3.18)	9.90 (5.13)	24.37 (10.50)
AUCT (ng•hr/mL)	2.63 (2.37)	6.84 (4.15)	18.68 (8.54)
AUC_{0-12} (ng•hr/mL)	1.73 (0.97)	3.31 (1.51)	7.11 (2.71)
Cmax (ng/mL)	0.95 (0.52)	1.62 (0.75)	3.57 (1.41)
Tmax (hr)a	0.50 (0.25-1.00)	0.50 (0.50-1.50)	0.50 (0.25-1.00)
$\lambda Lamda_z$ (hr^{-1})	0.1661 (0.1677)	0.0752 (0.0678)	0.0414 (0.0134)
t½ (hr)	7.27 (4.76)	13.72 (6.55)	18.35 (5.77)

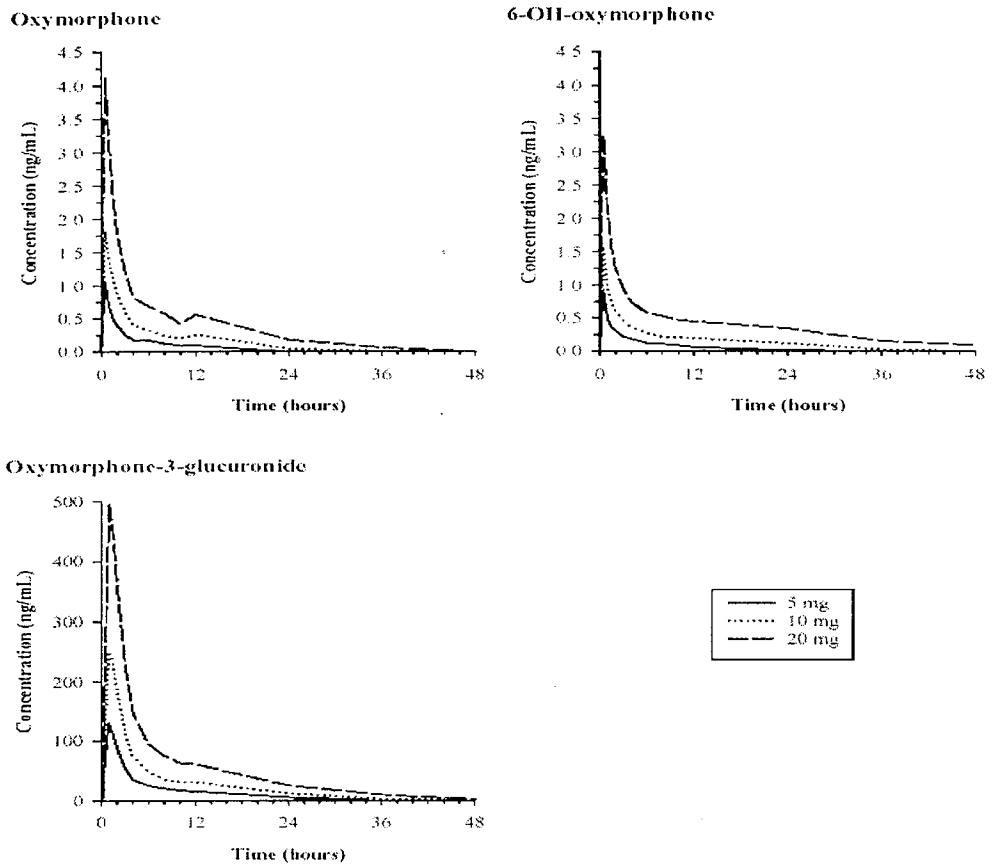
amedian (range)
OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone

Table - Analysis of Dose Proportionality Following Single-Dose Administration Normalized to 10 mg (Geometric Least Square Means and Standard Error):

PK Variable	5 mg	10 mg	20 mg	p-value
OXM				
ln-AUC (ng•hr/mL)	8.09 (1.05)	8.49 (1.05)	9.65 (1.05)	0.0627
ln-Cmax (ng/mL)	2.00 (1.06)	1.80 (1.06)	2.04 (1.06)	0.2124
6-OH-OXM				
ln-AUC (ng•hr/mL)	6.17 (1.08)	8.54 (1.08)	11.04 (1.08)	0.0000
ln-Cmax (ng/mL)	1.67 (1.06)	1.46 (1.06)	1.64 (1.06)	0.1888

OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone;

Figure - Mean IR single dose plasma concentration profiles:



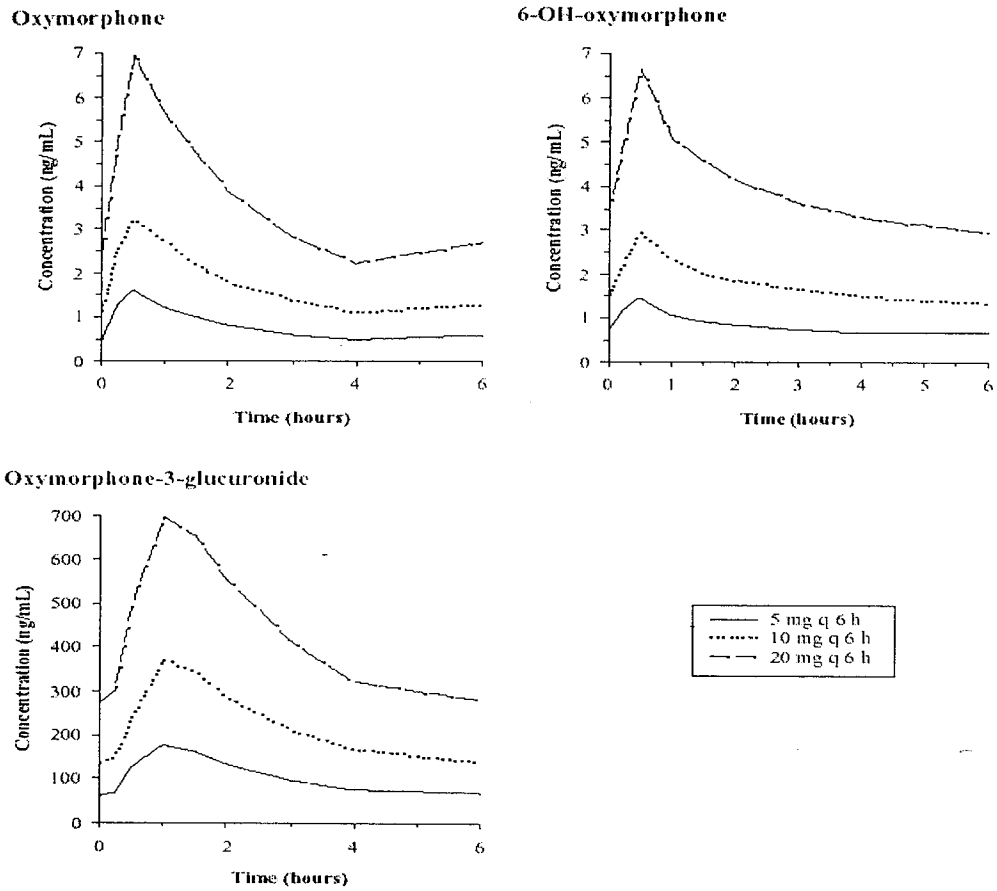
After multiple doses (for 7 days qid) of 5, 10 and 20 mg (2 x 10 mg) IR tablets, the data indicated that dose proportionality was achieved, however, for 10 and 20 mg IR tablets, the dose-normalized oxymorphone AUC was slightly greater than that of the 5 mg dose. Additionally the 20 mg dose-normalized 6-OH-oxymorphone AUC was slightly greater than that of the other two doses. However, it appears that the AUC is within 10 % the other two doses:

Table - Analysis of Dose Proportionality at Steady-State Normalized to 10 mg IR (on Day 8 measurement) :

Parameter	5 mg q 6 hr	10 mg q 6 hr	20 mg q 6 hr	p-value
OXM				
ln-AUCss (ng•hr/mL)	8.91 (1.03)	9.76 (1.03)	9.97 (1.03)	0.0600
ln-Cmax (ng/mL)	3.31 (1.05)	3.41 (1.05)	3.44 (1.05)	0.8338
6-OH-OXM				
ln-AUCss (ng•hr/mL)	9.14 (1.04)	9.99 (1.04)	10.83 (1.04)	0.0169
ln-Cmax (ng/mL)	2.91 (1.04)	2.94 (1.04)	3.19 (1.04)	0.1935

OXM=oxymorphone; 6-OH-OXM=6-OH-oxymorphone;

Figure - Mean Steady-State Plasma Concentrations of Oxymorphone and Metabolites Following 5 mg, 10 mg, or 20 mg Oxymorphone IR qid (on Day 8 measurement):



As a result, it is reasonable to conclude that the pharmacokinetics of oxymorphone and its metabolites are linear and dose-proportional following administration of oxymorphone IR tablets in doses ranging from 5 mg to 20 mg every 6 hours.

ER Tablets

After a single dose of 5, 10, 20 and 40 mg ER tablets, the data indicated that dose proportionality was achieved:

Figure - Mean Single-Dose Plasma Concentrations

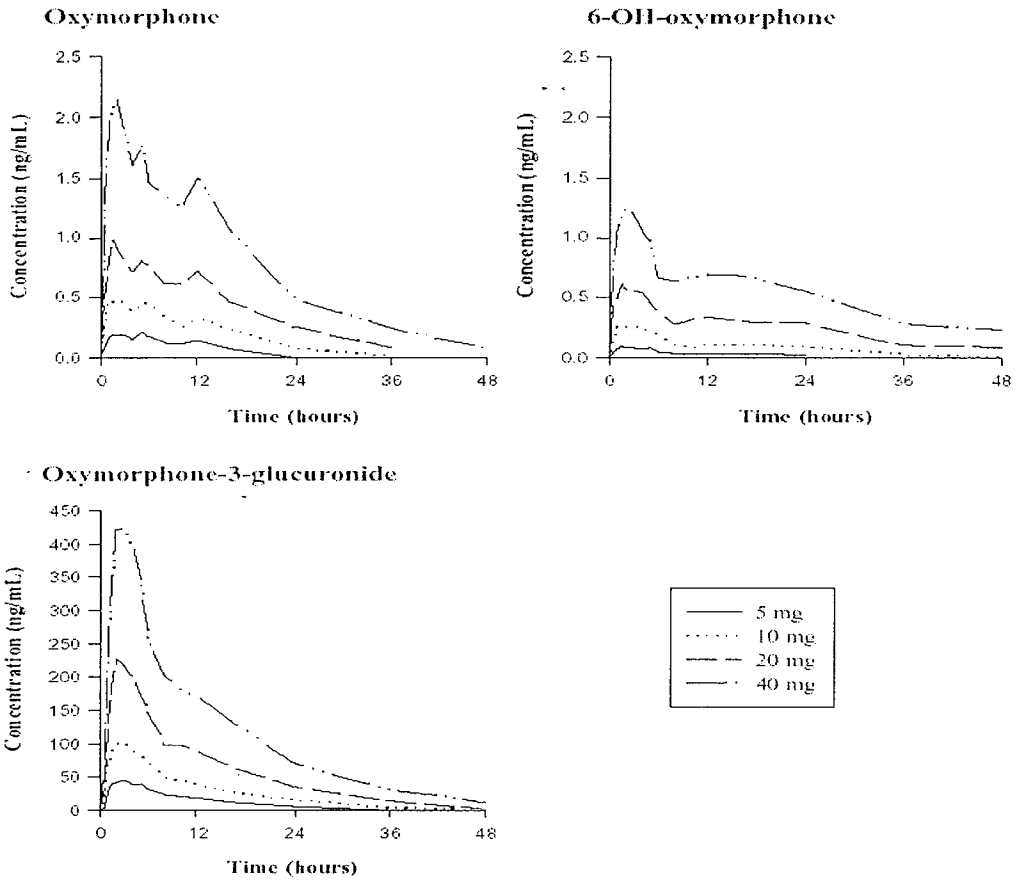


Table - Mean (SD) Single-Dose ER tablet Pharmacokinetic Results:

Variable	5 mg	10 mg	20 mg	40 mg
OXM				
AUCT (ng•hr/mL)	2.13 (1.28)	6.66 (3.55)	15.08 (6.95)	35.37 (16.19)
AUC (ng•hr/mL)	4.54 (2.04)	8.94 (4.16)	17.80 (7.22)	37.90 (16.20)
AUC0-12 (ng•hr/mL)	1.74 (0.94)	4.44 (1.70)	8.50 (4.04)	18.47 (9.98)
Cmax (ng/mL)	0.27 (0.13)	0.65 (0.29)	1.21 (0.77)	2.59 (1.65)
Tmax (hr)[a]	3.00 (1.00–12.00)	3.00 (0.50–6.00)	4.00 (1.00–12.00)	2.50 (0.50–12.00)
CL/F (L/min.)	26.36 (25.21)	22.26 (9.27)	20.93 (6.46)	19.44 (5.06)
t½ (hr)	11.30 (10.81)	9.83 (5.68)	9.89 (3.21)	9.35 (2.94)
a : median				
6-OH-OXM				
AUCT (ng•hr/mL)	0.88 (1.40)	3.64 (3.68)	11.26 (7.19)	25.52 (13.28)
AUC (ng•hr/mL)	5.80 (4.99)	6.94 (6.79)	16.12 (9.47)	32.79 (18.13)
AUC0-12 (ng•hr/mL)	0.59 (0.89)	1.95 (1.30)	4.88 (2.12)	9.92 (5.10)
Cmax (ng/mL)	0.14 (0.12)	0.37 (0.19)	0.80 (0.33)	1.44 (0.56)
Tmax (hr)[a]	3.50 (1.00–12.00)	2.00 (0.50–6.00)	1.50 (0.50–12.00)	2.00 (1.00–12.00)
T½ (hr)	16.96 (16.67)	13.40 (11.53)	16.82 (6.59)	18.44 (7.88)
[a]median (range)				
OXM=oxymorphone				

Table - Analysis of Dose Proportionality Following Single-Dose Administration Normalized to 20 mg (geometric least square means and standard error):

Parameter	5 mg	10 mg	20 mg	40 mg	p-value
OXM					
ln-AUC (ng•hr/mL)	15.74 (1.12)	16.53 (1.11)	17.72 (1.11)	17.54 (1.11)	0.7766
ln-Cmax (ng/mL)	1.04 (1.11)	1.12 (1.11)	1.10 (1.11)	1.19 (1.11)	0.5574
ln-CL/F (L/min.)	21.18 (1.12)	20.16 (1.11)	18.81 (1.11)	19.01 (1.11)	0.7766
6-OH-OXM					
ln-AUC (ng•hr/mL)	10.98 (1.36)	8.41 (1.23)	12.73 (1.23)	13.80 (1.23)	0.1590
ln-Cmax (ng/mL)	0.63 (1.13)	0.64 (1.12)	0.74 (1.12)	0.68 (1.12)	0.5031

OXM=oxymorphone
6-OH-OXM=6-OH-oxymorphone

After multiple doses (for 8 days bid) of 5, 10, 20 and 40 mg ER tablets, the data indicated that dose proportionality was achieved.

Figure - Mean Steady-State Plasma Concentrations:

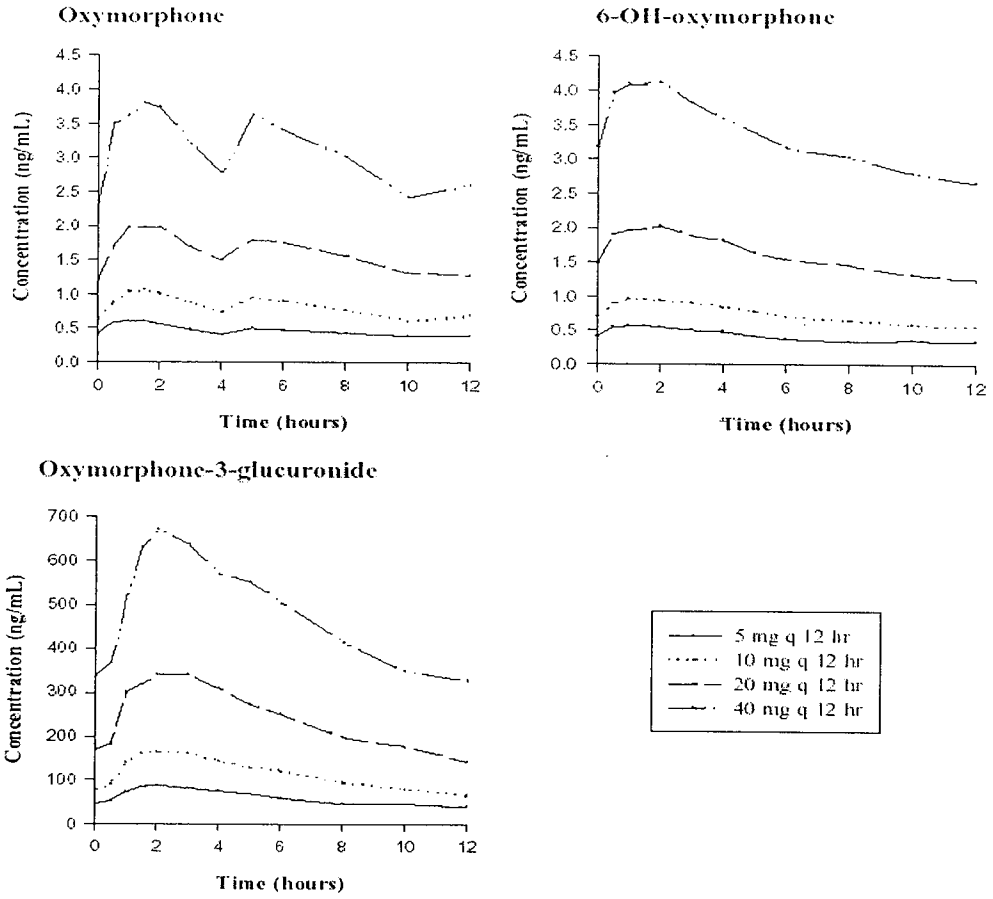


Table - Mean (SD) Steady-State Pharmacokinetic Results:

Variable	5 mg q 12 hr	10 mg q 12 hr	20 mg q 12 hr	40 mg q 12 hr
OXM				
AUCss (ng•hr/mL)	5.60 (3.87)	9.77 (3.52)	19.28 (8.32)	36.98 (13.53)
Cmax (ng/mL)	0.70 (0.55)	1.24 (0.56)	2.54 (1.35)	4.47 (1.91)
Tmax (hr)[a]	1.50 (0.50–12.00)	2.00 (0.50–12.00)	1.25 (0.50–6.00)	3.50 (0.50–10.00)
CL/F (L/min.)	18.18 (6.31)	19.33 (7.29)	20.23 (7.96)	19.76 (5.57)
Cmin (ng/mL)	0.41 (0.59)	0.64 (0.26)	1.22 (0.52)	2.33 (1.16)
Cavg (ng/mL)	0.47 (0.32)	0.81 (0.29)	1.61 (0.69)	3.08 (1.13)
FI	0.71 (0.27)	0.69 (0.24)	0.78 (0.57)	0.68 (0.23)
R	3.43 (1.65)	2.29 (0.62)	2.39 (0.75)	2.13 (0.52)
a: median				
6-OH-OXM				
AUCss (ng•hr/mL)	5.06 (3.77)	8.87 (3.83)	19.24 (10.09)	39.70 (19.87)
Cmax (ng/mL)	0.62 (0.46)	1.05 (0.44)	2.26 (1.12)	4.55 (2.24)
Tmax (hr)[a]	1.50 (0.50–12.00)	1.00 (0.50–4.00)	1.50 (0.50–12.00)	1.25 (0.50–10.00)
Cmin (ng/mL)	0.42 (0.45)	0.70 (0.31)	1.48 (0.76)	3.17 (1.73)
Cavg (ng/mL)	0.42 (0.31)	0.74 (0.32)	1.60 (0.84)	3.31 (1.66)
FI	0.75 (0.80)	0.48 (0.22)	0.50 (0.17)	0.44 (0.16)
R	26.27 (27.76)	7.05 (6.09)	4.23 (1.85)	4.11 (1.15)

OXM=oxymorphone 6-OH-OXM=6-OH-oxymorphone
[a]median (range) R = accumulation ratio FI = fluctuation index

Table - Analysis of Dose Proportionality at Steady -State Normalized to 20 mg (geometric least square means and standard error):

Parameter	5 mg q 12 hr	10 mg q 12 hr	20 mg q 12 hr	40 mg q 12 hr	p-value
OXM					
ln-AUCss (ng•hr/mL)	19.16 (1.09)	18.16 (1.10)	18.12 (1.10)	18.24 (1.10)	0.9229
ln-Cmax (ng/mL)	2.32 (1.10)	2.14 (1.10)	2.32 (1.10)	2.23 (1.10)	0.8109
ln-CL/F (L/min.)	17.40 (1.09)	18.36 (1.10)	18.39 (1.10)	18.27 (1.10)	0.9229
6-OH-OXM					
ln-AUCss (ng•hr/mL)	14.96 (1.13)	16.34 (1.13)	17.56 (1.13)	18.89 (1.13)	0.2132
ln-Cmax (ng/mL)	1.92 (1.11)	1.90 (1.11)	2.07 (1.11)	2.18 (1.12)	0.4104
OXM=oxymorphone					

Would dose-normalized oxymorphone exposure comparable after 20 mg ER (1 x 20 mg) and 10 mg IR ?

After a single dose of 10 mg IR and 20 mg ER administration, the data indicated that dose-normalized AUC were comparable. However, as expected the dose-normalized Cmax for ER was significantly lower than that of the IR tablets.

Figure - **Average Single-Dose Plasma Concentrations (All Subjects)**

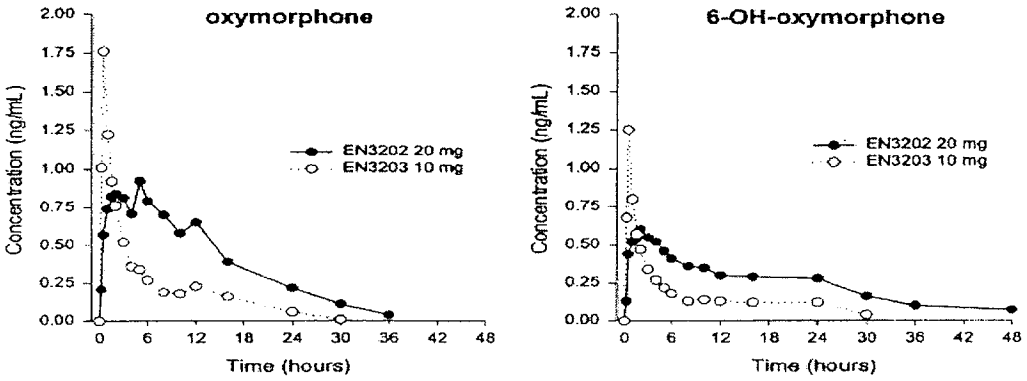


Figure - **Average Oxymorphone and 6-OH-oxymorphone Plasma Concentrations (0 – 12 hours)**

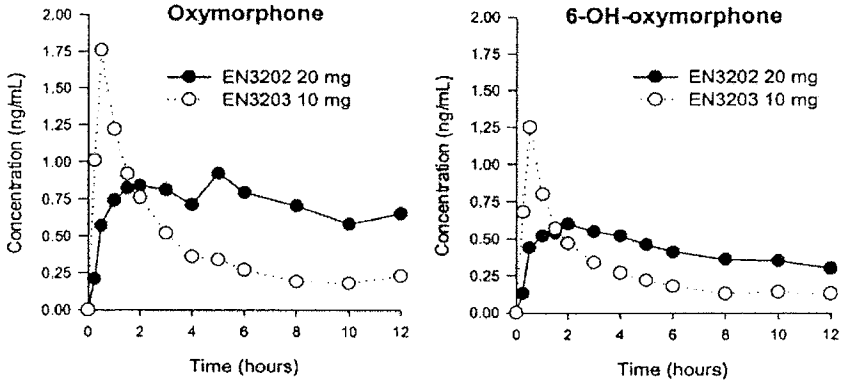


Table - Analysis of IR and ER tablet exposure after single dose administration - Normalized to 20 mg (Least Square Means and 90% confidence intervals):

Variable	EN3202 (Test)	EN3203* (Reference)	Ratio	Lower 90% C.I.	Upper 90% C.I.
Oxymorphone					
ln-AUCT (ng•hr/mL)	14.20	13.55	1.0474	0.9480	1.1572
ln-AUC (ng•hr/mL)	14.80	14.71	1.0060	0.8995	1.1252
ln-C_{max} (ng/mL)	1.06	3.55	0.2988	0.2518	0.3545
6-OH-oxymorphone					
ln-AUCT (ng•hr/mL)	10.46	10.24	1.0219	0.9371	1.1143
ln-AUC (ng•hr/mL)	14.31	13.98	1.0235	0.8623	1.2149
ln-C_{max} (ng/mL)	0.66	2.58	0.2548	0.2258	0.2874

*Dose of immediate-release normalized to 20 mg
Analysis using average bioequivalence approach on ln-transformed data for all subjects

Therefore, it is reasonable to assume that similar exposure will be obtained if a same strength single dose IR and ER tablets are admistered. Additionally, after multiple doses (for 8 days) of 10 mg IR tablets (qid) and 20 mg ER tablets (bid), the data indicated that dose-normalized AUC were comparable. However, once again, as expected the dose-normalized Cmax for ER was significantly lower than that of the IR tablets.

Figure - Mean Steady-State Plasma Concentrations Following Administration of Oxymorphone ER Tablets 20 mg Every 12 Hours and Oxymorphone IR Tablets 10 mg Every 6 Hours (on Day 9 measurement):

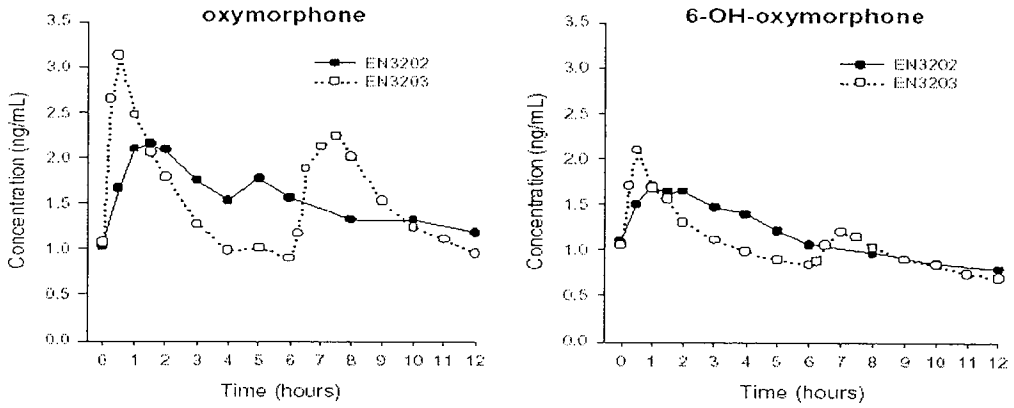


Table - Analysis of IR and ER exposure at Steady-State (Normalized to 20 mg on Day 9 measurement):

Variable	EN3202 (Test)	EN3203* (Reference)	Ratio	Lower 90% C.I.	Upper 90% C.I.
Oxymorphone					
ln-AUC_{ss} (ng•hr/mL)	17.70	16.74	1.0576	0.9070	1.2331
ln-C_{max} (ng/mL)	2.44	3.10	0.7849	0.6469	0.9524
ln-FI	0.91	1.48	0.6167	0.4484	0.8482
ln-Swing	1.45	2.41	0.6001	0.3660	0.9839
6-OH-oxymorphone					
ln-AUC_{ss} (ng•hr/mL)	12.40	11.19	1.1077	0.9507	1.2907
ln-C_{max} (ng/mL)	1.64	2.05	0.7959	0.6776	0.9349
ln-FI	0.69	1.02	0.6749	0.4894	0.9308
ln-Swing	0.78	1.30	0.6018	0.4003	0.9045

*AUC results combined for two 10 mg doses; C_{max} = first dose
Analysis using average bioequivalence approach

In all, as expected, the oxymorphone plasma concentrations following administration of oxymorphone ER tablets was characterized by lower peak plasma concentrations and higher plateau concentrations than oxymorphone IR tablets.

The average trough concentrations indicated that steady-state was achieved after six days of administration. However, there is an indication that the trough oxymorphone concentrations were at approximately 90% of the steady-state values on the second day of multiple dosing. There was little to no oxymorphone accumulation after multiple doses.

Table - Average Trough plasma concentration (Day 4 through Day 9):

Analyte	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Oxymorphone						
EN3202	1.096	1.123	1.197	1.189	1.187	1.028
EN3203	0.748	0.837	0.916	0.915	0.862	1.073
6-OH-oxymorphone						
EN3202	0.893	1.147	1.150	1.274	1.288	1.087
EN3203	0.723	0.884	0.872	1.005	0.983	1.046

Table - Mean (SD) accumulation ratio after multiple administration

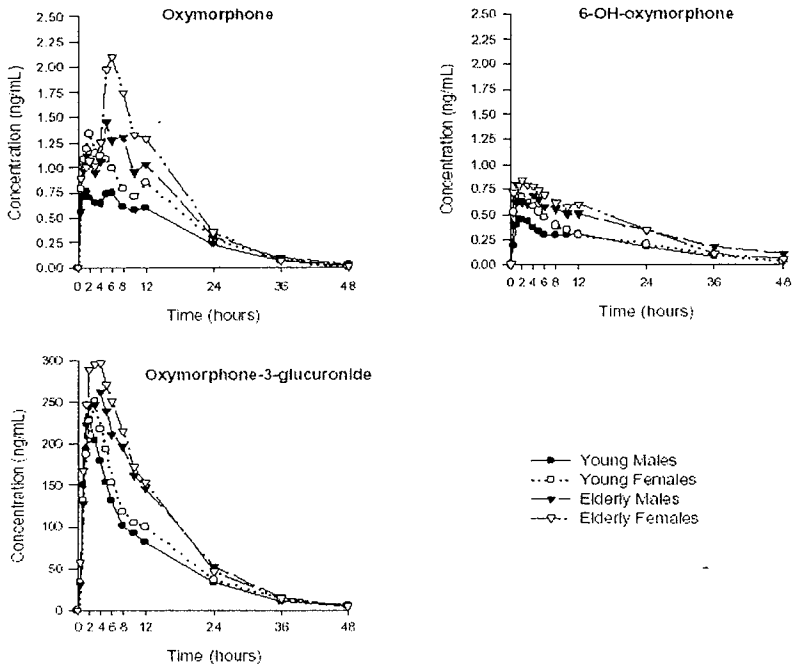
Variable	EN3202	EN3203
Oxymorphone		
R (AUC)	2.24 (0.94)	2.41 (0.96)
R (Cmax)	2.40 (0.92)	2.12 (1.36)
T½ effective (hr)	13.91 (8.05)	8.04 (3.80)
6-OH-oxymorphone		
R (AUC)	2.86 (1.30)	2.90 (1.25)
R (Cmax)	2.78 (1.25)	1.84 (0.86)
T½ effective (hr)	19.95 (10.70)	10.23 (4.94)

R = accumulation ratio (e.g., AUC_{ss}/AUC_1)

Are there any gender and age effects after ER tablet administration?

The effect of age and gender was evaluated following single- and multiple-doses of oxymorphone ER tablets in adult volunteers (4 groups : young males 18-40 years, young females 18-40 years, elderly males ≥65 years, and elderly females ≥65 years).
The single-dose and steady-state plasma concentrations of oxymorphone and 6-OH-oxymorphone were approximately 40% higher in elderly subjects (≥65 years of age) than in young subjects (20 to 40 years of age).

Figure - Mean Single-Dose Plasma Concentrations in Young and Elderly Men and Women Following Administration of Oxymorphone ER 20 mg:



The average plasma concentrations at steady-state showed the same relationship between treatment groups seen for the single-dose.

Figure - Mean Steady-State Plasma Concentrations Following Administration of Oxymorphone ER 20 mg Every 12 Hours in Young and Elderly Men and Women:

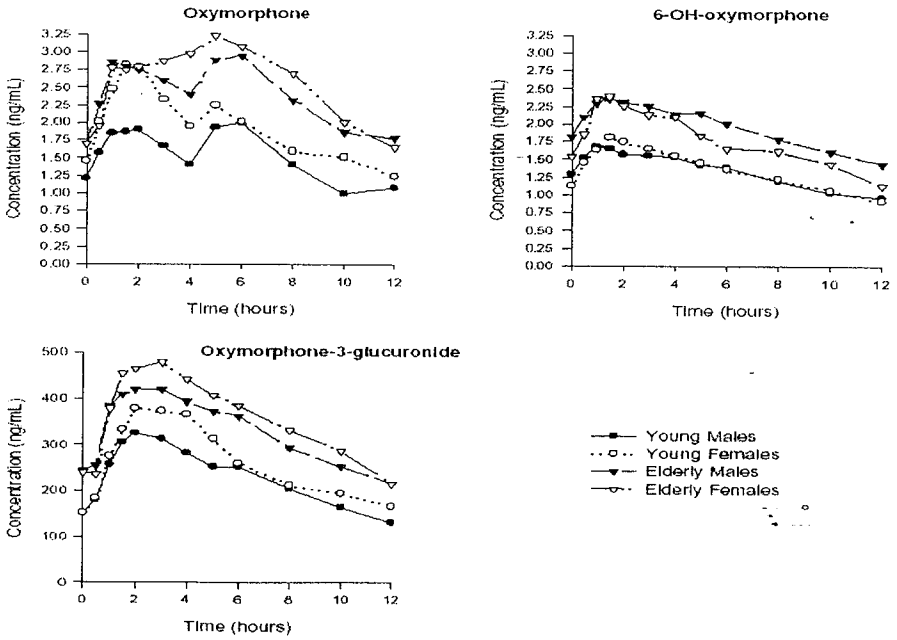


Table - Mean (SD) Single-Dose Pharmacokinetic Results:

Parameter	Young Males	Young Females	Elderly Males	Elderly Females
Oxymorphone				
Cmax (ng/mL)	1.00 (0.33)	1.57 (0.60)	1.62 (0.75)	2.28 (1.52)
Tmax (hr)*	3.0 (0.5-8.0)	2.0 (1.0-12.0)	6.0 (2.0-12.0)	6.0 (1.0-10.0)
AUCT (ng•hr/mL)	14.81 (4.07)	20.23 (8.95)	23.98 (8.29)	29.69 (17.60)
AUC (ng•hr/mL)	18.15 (6.06)	22.54 (8.63)	25.62 (8.40)	32.31 (18.38)
T½ (hr)	11.56 (5.26)	9.42 (3.71)	7.92 (2.34)	7.54 (1.85)
a: median				
6-OH-oxymorphone				
Cmax (ng/mL)	0.56 (0.17)	0.89 (0.54)	0.79 (0.27)	0.98 (0.31)
Tmax (hr)*	2.0 (1.5-12.0)	1.5 (0.5-4.0)	3.5 (1.0-12.0)	3.0 (0.5-6.0)
AUCT (ng•hr/mL)	8.45 (3.37)	10.91 (6.30)	16.67 (4.30)	17.58 (9.09)
AUC (ng•hr/mL)	12.99 (5.18)	16.85 (6.91)	20.54 (5.64)	24.55 (16.70)
T½ (hr)	19.77 (15.52)	29.38 (27.31)	17.95 (7.93)	15.77 (7.46)
a: median				

Table - Analysis of Single-Dose Oxymorphone Pharmacokinetic Results (geometric least square means)

Variable	(Test)	(Reference)	Ratio	Lower 90% C.I.	Upper 90% C.I.
	Elderly	Young			
Ln-AUC (ng•hr/mL)	26.19	19.19	1.36	1.19	1.57
Ln-AUCT (ng•hr/mL)	24.12	16.40	1.47	1.27	1.70
Ln-Cmax (ng/mL)	1.71	1.18	1.45	1.25	1.69
	Female	Male			
Ln-AUC (ng•hr/mL)	24.44	20.56	1.19	1.03	1.37
Ln-AUCT (ng•hr/mL)	21.94	18.02	1.22	1.05	1.40
Ln-Cmax (ng/mL)	1.69	1.19	1.43	1.23	1.66
	Elderly Female	Young Female			
Ln-AUC (ng•hr/mL)	28.08	21.27	1.32	1.15	1.52
Ln-AUCT (ng•hr/mL)	25.59	18.80	1.36	1.18	1.57
Ln-Cmax (ng/mL)	1.97	1.46	1.35	1.17	1.57
	Elderly Male	Young Male			
Ln-AUC (ng•hr/mL)	24.43	17.31	1.41	1.23	1.62
Ln-AUCT (ng•hr/mL)	22.73	14.30	1.59	1.38	1.83
Ln-Cmax (ng/mL)	1.48	0.95	1.55	1.34	1.81
	Young Female	Young Male			
Ln-AUC (ng•hr/mL)	21.27	17.31	1.23	1.07	1.41
Ln-AUCT (ng•hr/mL)	18.80	14.30	1.32	1.14	1.52
Ln-Cmax (ng/mL)	1.46	0.95	1.53	1.31	1.77
	Elderly Female	Elderly Male			
Ln-AUC (ng•hr/mL)	28.08	24.43	1.15	1.00	1.32
Ln-AUCT (ng•hr/mL)	25.59	22.73	1.13	0.98	1.30
Ln-Cmax (ng/mL)	1.97	1.48	1.33	1.15	1.55

Analysis on ln-transformed data; model: pkvar = age + gender + age*gender
Excluding Subject 10

On average, age greater than 65 years was associated with a 1.4-fold increase in oxymorphone AUC and a 1.5-fold increase in Cmax.

Table - Analysis of Single-Dose 6-OH-oxymorphone Pharmacokinetic Results

Variable	(Test)	(Reference)	Ratio	Lower 90% C.I.	Upper 90% C.I.
	Elderly	Young			
ln-AUC (ng•hr/mL)	20.15	13.49	1.4935	1.2616	1.7681
ln-AUCT (ng•hr/mL)	15.81	8.59	1.8417	1.5641	2.1685
ln-Cmax (ng/mL)	0.83	0.65	1.2846	1.1243	1.4677
	Female	Male			
ln-AUC (ng•hr/mL)	17.62	15.43	1.1422	0.9648	1.3521
ln-AUCT (ng•hr/mL)	12.03	11.29	1.0652	0.9046	1.2542
ln-Cmax (ng/mL)	0.85	0.63	1.3451	1.1773	1.5369

Analysis on ln-transformed data; model: pkvar = age + gender + age*gender

The 6-OH-oxymorphone AUC was 1.5-fold higher in elderly subjects than in young subjects, and Cmax was increased 1.3-fold. While the 6-OH-oxymorphone Cmax was approximately 1.4-fold higher in females than males, the difference in AUC associated with gender was small.

Table - Mean (SD) Steady-State Pharmacokinetic Results: Oxymorphone

Parameter	Young Males	Young Females	Elderly Males	Elderly Females
Oxymorphone				
Cmax (ng/mL)	2.41 (0.72)	3.16 (1.13)	3.53 (1.45)	4.25 (2.69)
Tmax (hr)*	2.5 (0.5-6.0)	1.8 (0.5-6.0)	3.5 (1.0-6.0)	5.0 (1.0-8.0)
AUCss (ng•hr/mL)	18.29 (4.89)	23.10 (7.94)	28.89 (11.35)	30.99 (15.93)
Swing	0.97 (0.80)	1.32 (1.06)	1.16 (0.62)	1.98 (2.14)
Fluctuation Index	0.87 (0.54)	0.92 (0.39)	0.77 (0.32)	0.94 (0.35)
Plateau Duration (hr)*	7.8 (2.0-12.0)	8.5 (5.0-12.0)	11.0 (4.0-12.0)	9.0 (3.0-12.0)
6-OH-oxymorphone				
Cmax (ng/mL)	1.85 (0.92)	2.04 (0.78)	2.59 (0.78)	2.71 (1.53)
Tmax (hr)*	1.5 (1.0-8.0)	1.5 (0.5-6.0)	1.5 (0.5-6.0)	2.0 (1.0-8.0)
AUCss (ng•hr/mL)	15.99 (8.75)	16.29 (8.84)	23.34 (7.42)	21.20 (13.82)
Swing	0.76 (0.72)	1.36 (1.43)	0.52 (0.36)	1.20 (1.03)
Fluctuation Index	0.53 (0.33)	0.83 (0.56)	0.43 (0.29)	0.78 (0.38)
Plateau Duration (hr)*	11.3 (6.0-12.0)	9.8 (2.5-12.0)	12.0 (6.0-12.0)	10.0 (6.0-12.0)

*median (range)

At steady-state, mean AUCss and Cmax results in the two elderly treatment groups greater than the younger subjects for oxymorphone and both metabolites.

There also appears to be a consistent tendency for female subjects to have higher AUCss and Cmax values than male subjects, regardless of age.

Table - Analysis of Age and Gender at Steady-State (geometric least square means):

Variable	(Test)	(Reference)	Ratio	Lower 90% C.I.	Upper 90% C.I.
Oxymorphone					
	Elderly	Young			
AUCss (ng•hr/mL)	27.57	19.66	1.41	1.24	1.59
Cmax (ng/mL)	3.51	2.62	1.34	1.17	1.53
	Female	Male			
AUCss (ng•hr/mL)	24.85	21.82	1.14	1.00	1.29
Cmax (ng/mL)	3.34	2.75	1.22	1.06	1.39
6-OH-oxymorphone					
	Elderly	Young			
AUCss (ng•hr/mL)	19.91	14.13	1.41	1.18	1.69
Cmax (ng/mL)	2.40	1.77	1.36	1.15	1.59
	Female	Male			
AUCss (ng•hr/mL)	16.09	17.48	0.92	0.77	1.10
Cmax (ng/mL)	2.11	2.01	1.05	0.89	1.24

Analysis on ln-transformed data; model: pkvar = age + gender + age*gender

AUCss values for oxymorphone and both metabolites in the elderly subjects were greater than the younger subjects by an average of approximately 40%. Similarly, the mean Cmax values in elderly subjects were greater than the younger subjects by approximately 30%–35%.

To explore the potential effect of body weight on the differences associated with age and gender, the steady-state AUC and Cmax results were analyzed following normalization to a constant dose level of 20 mg per 70 kg body weight:

Table - Comparison of Age and Gender Analyses Results for Single-Dose and Steady-State (ratio of LS Means and 90% confidence intervals)

		Single-Dose	**Steady-State**	**Steady-State (normalized 20mg/70kg)**
Oxymorphone				
Age	AUC	1.36 (1.19–1.57)	1.40 (1.24–1.59)	1.38 (1.22–1.56)
	Cmax	1.45 (1.25–1.69)	1.34 (1.17–1.53)	1.32 (1.15–1.50)
Gender	AUC	1.19 (1.03–1.37)	1.14 (1.00–1.29)	0.98 (0.87–1.11)
	Cmax	1.43 (1.23–1.66)	1.21 (1.06–1.39)	1.05 (0.92–1.19)
6-OH-oxymorphone				
Age	AUC	1.49 (1.26–1.77)	1.41 (1.18–1.69)	1.39 (1.15–1.67)
	Cmax	1.28 (1.12–1.47)	1.36 (1.15–1.59)	1.33 (1.13–1.58)
Gender	AUC	1.14 (0.97–1.35)	0.92 (0.77–1.10)	0.79 (0.66–0.96)
	Cmax	1.35 (1.18–1.54)	1.05 (0.89–1.24)	0.91 (0.77–1.07)

Normalization of the data to a dose of 20 mg per 70 kg does not appear to have any significant impact on the differences associated with age.

Overall, The elderly subjects had higher average AUC and Cmax values for all three species than the young subjects; and females were higher than males. The mean oxymorphone AUC in elderly females exceed the result in elderly males by approximately 26%; and the AUC in young females exceed the result in young males by approximately the same amount (24%). Similar differences were observed for 6-OH-oxymorphone.

Is dosage adjustment needed due to hepatic impairment after ER tablet administration?

The effect of hepatic impairment was assessed following a single administration of 20 oxymorphone ER tablet.

Figure - Mean Plasma Oxymorphone, 6-OH-oxymorphone, and Oxymorphone-3-glucuronide Concentrations Following Administration of Oxymorphone ER 20 mg

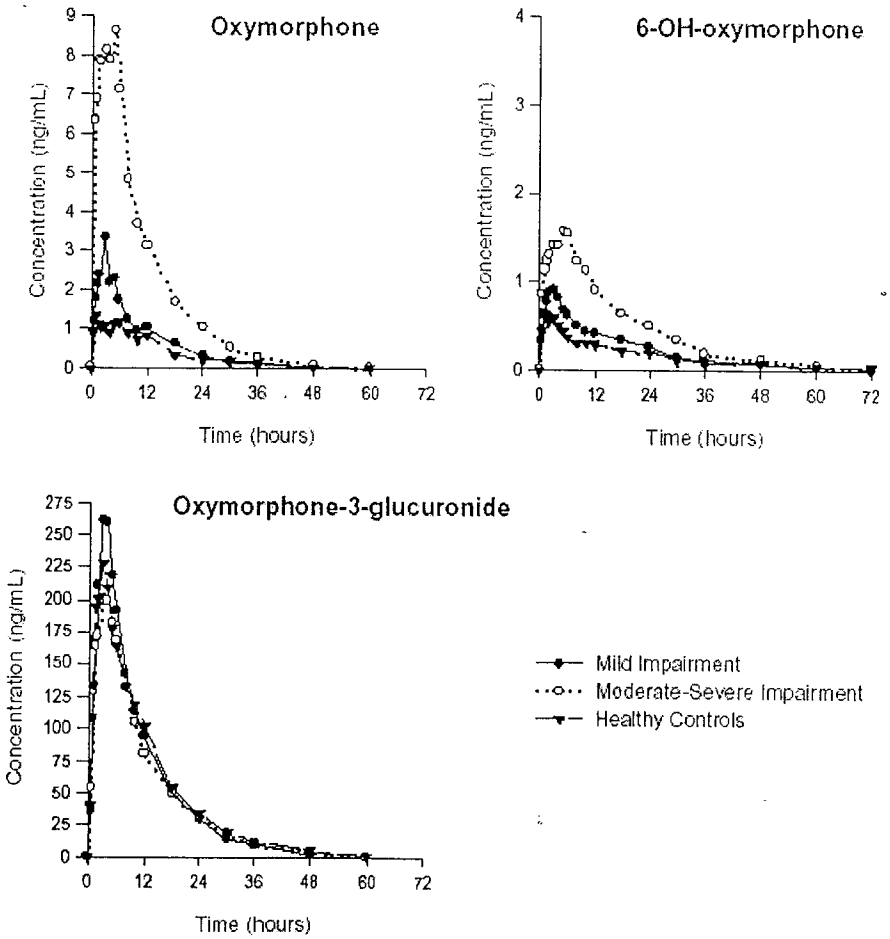


Table - **Mean (SD) Plasma Pharmacokinetic Results**

Analyte/Variable	Mild Impairment	Moderate-Severe Impairment	Healthy Controls
Oxymorphone			
AUC (ng•hr/mL)	32.10 (21.71)	105.57 (108.92)	20.58 (9.02)
AUCT (ng•hr/mL)	29.96 (21.79)	103.66 (108.86)	17.96 (7.69)
C_{max} (ng/mL)	3.98 (4.06)	9.16 (9.76)	1.73 (0.68)
T_{max} (hr)*	1.75 (0.5 – 5.0)	1.5 (0.5 – 5.0)	3.5 (1.0 –12.0)
λ_z (hr^{-1})	0.0830 (0.0392)	0.0970 (0.0365)	0.0970 (0.0540)
T1/2 (hr)	11.82 (9.34)	8.04 (2.90)	9.98 (6.35)
CL/F (L/min)	13.30 (5.81)	7.17 (5.08)	21.15 (13.54)
6-OH-oxymorphone			
AUC (ng•hr/mL)	17.35 (11.17)	32.12 (19.80)	14.76 (11.51)
AUCT (ng•hr/mL)	14.11 (9.73)	29.25 (20.17)	10.80 (9.65)
C_{max} (ng/mL)	1.12 (0.79)	1.78 (1.00)	0.72 (0.32)
T_{max} (hr)*	1.25 (0.5 – 3.0)	1.75 (1.0 – 6.0)	1.25 (1.0 – 4.0)
λ_z (hr^{-1})	0.0545 (0.0269)	0.0632 (0.0303)	0.0532 (0.0356)
T1/2 (hr)	17.54 (13.12)	13.87 (8.02)	19.19 (11.75)
Oxymorphone-3-glucuronide			
AUC (ng•hr/mL)	2954.1 (1136.2)	2713.9 (1498.6)	2979.6 (896.1)
AUCT (ng•hr/mL)	2836.7 (1091.9)	2629.3 (1457.8)	2886.8 (883.9)
C_{max} (ng/mL)	274.1 (95.8)	212.0 (100.5)	234.3 (41.7)
T_{max} (hr)*	3.0 (3.0 – 4.0)	3.5 (3.0 – 4.0)	3.0 (1.5 – 4.0)
λ_z (hr^{-1})	0.0974 (0.0367)	0.1075 (0.0435)	0.0859 (0.0264)
T1/2 (hr)	8.21 (3.87)	7.40 (2.98)	8.89 (3.00)

*median (range)

Individuals with mild liver disease did not appear to have a significant increase (approx. 1.5-fold increase). The data also indicated that individual oxymorphone AUC values varied across a 5- fold range (6.2 to 33.9 ng•hr/mL) in healthy controls, a 5-fold range (15.4 to 74.8 ng•hr/mL) in subjects with mild disease, and a 10- fold range (24.9 to 250.3 ng•hr/mL) in subjects with moderate-severe disease. The mean plasma AUC and Cmax for 6-OH-oxymorphone was increased approximately 2.3- fold relative to the healthy control group in subjects with moderate or severe hepatic impairment. Conversion of oxymorphone to 6-OH-oxymorphone appears to be reduced in subjects with moderate-severe impairment. There was no change in t1/2 of oxymorphone among all three groups.

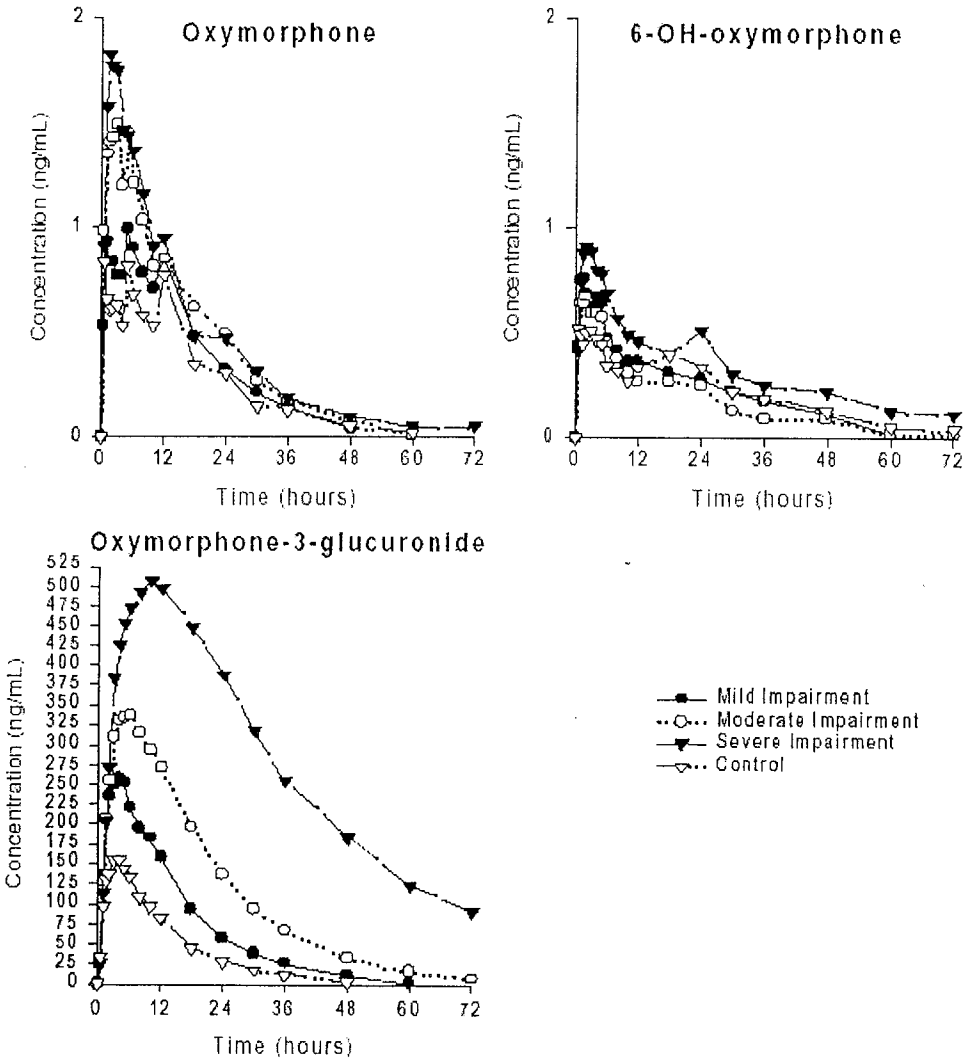
With respect to 'severe' patients, it is noted that the "moderate-severe" category included 5 subjects in Child-Pugh Class B and 1 subject in Class C. The 1 subject in Child-Pugh Class C had Cmax and AUC values of 23.6 ng/mL and 250.3 ng•hr/mL, respectively. The AUC in this subject represents an approximately 12.2-fold increase in bioavailability. For moderately impaired subjects, the AUC was increased up to 3.7-fold (mean value).

Titration needs to be undertaken with extreme caution in moderately impaired subjects. Oxymorphone should be contraindicated in severely impaired subjects. It is noted that the Applicant previously proposed contraindication for the severe hepatic impairment (I 56919 serial # 146; submission date 5/23/02).

Is dosage adjustment needed due to renal impairment?

The effect of renal impairment was assessed following a single oral dose of 20 mg oxymorphone ER in renal impaired subjects (8 healthy and 24 renally impaired subjects)

Figure - Mean Plasma Concentrations in Subjects With Normal and Impaired Renal Function



In general, the renal impaired subjects had higher mean plasma oxymorphone concentrations compared with control group during the first 12 hours after dose administration. There was less clear separation in mean 6-OH-oxymorphone between the mild and moderately impaired groups relative to the healthy controls.

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Table - Summary of Mean (SD) Single-Dose Plasma Pharmacokinetic Parameters (Untransformed) in Subjects With Normal and Impaired Renal Function–ER Tablet 20 mg:

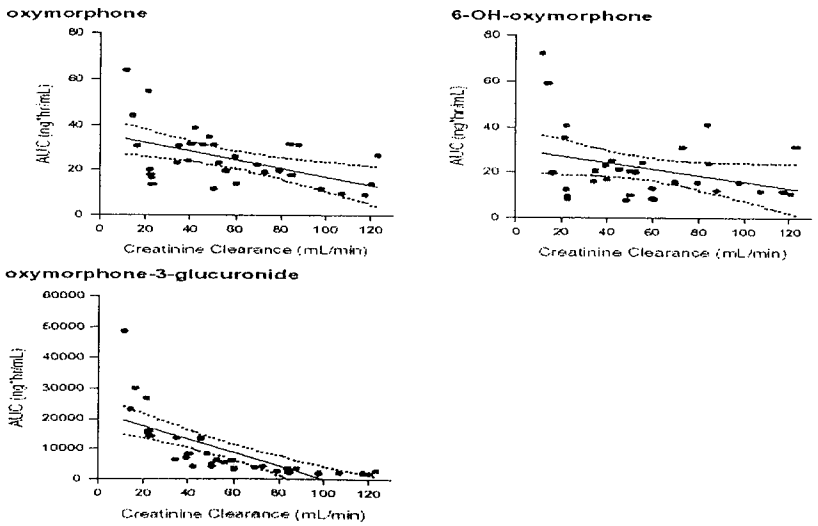
Analyte/Variable	Mild Impairment	Moderate Impairment	Severe Impairment	Healthy Controls
Oxymorphone				
AUC (ng•hr/mL)	21.68 (5.07)	27.93 (8.34)	32.46 (19.12)	18.86 (9.39)
AUCT (ng•hr/mL)	19.00 (6.26)	26.09 (8.01)	29.72 (17.35)	15.79 (9.46)
Cmax (ng/mL)	1.47 (0.54)	1.75 (0.59)	2.04 (1.07)	1.16 (0.71)
Tmax (hr)*	3.5 (1.0 12.0)	2.0 (0.5 5.0)	2.0 (1.0 8.0)	3.5 (0.5 12.0)
CLo (L/min.)	16.14 (3.94)	13.53 (6.52)	13.79 (7.29)	22.07 (10.56)
t½ (hr)	12.42 (5.10)	9.92 (2.45)	13.35 (9.45)	13.46 (3.38)
6-OH-oxymorphone				
AUC (ng•hr/mL)	18.57 (6.91)	17.64 (6.12)	32.04 (23.82)	19.76 (11.17)
AUCT (ng•hr/mL)	14.26 (4.39)	11.70 (6.09)	26.48 (21.36)	14.95 (10.58)
Cmax (ng/mL)	0.99 (0.30)	0.76 (0.31)	0.99 (0.55)	0.70 (0.34)
Tmax (hr)*	1.5 (1.0 4.0)	2.5 (0.5 5.0)	2.0 (1.0 4.0)	1.5 (0.5 18.0)
t½ (hr)	18.04 (9.92)	27.82 (14.10)	26.53 (13.91)	22.20 (10.76)

*median (range)

Mean oxymorphone AUC and Cmax increased progressively as renal function declined, but the elimination half-life appeared unaffected by renal impairment. The mean impaired-to-control ratios (90% confidence intervals) for oxymorphone ln-AUC were 1.26 (0.86-1.84), 1.57 (1.07-2.31), and 1.65 (1.13-2.42) in subjects with mild, moderate, and severe renal impairment, respectively. Additionally, the corresponding results for oxymorphone ln-Cmax were 1.38 (0.94-2.03), 1.65 (1.12-2.43), and 1.80 (1.23-2.65), respectively.

With respect to correlation between creatinine clearance and oxymorphone exposure, there was a statistically significant correlation between creatinine clearance and the AUC for oxymorphone, but, not with 6-OH-oxymorphone:

Figure - Relationship Between AUC and Creatinine Clearance



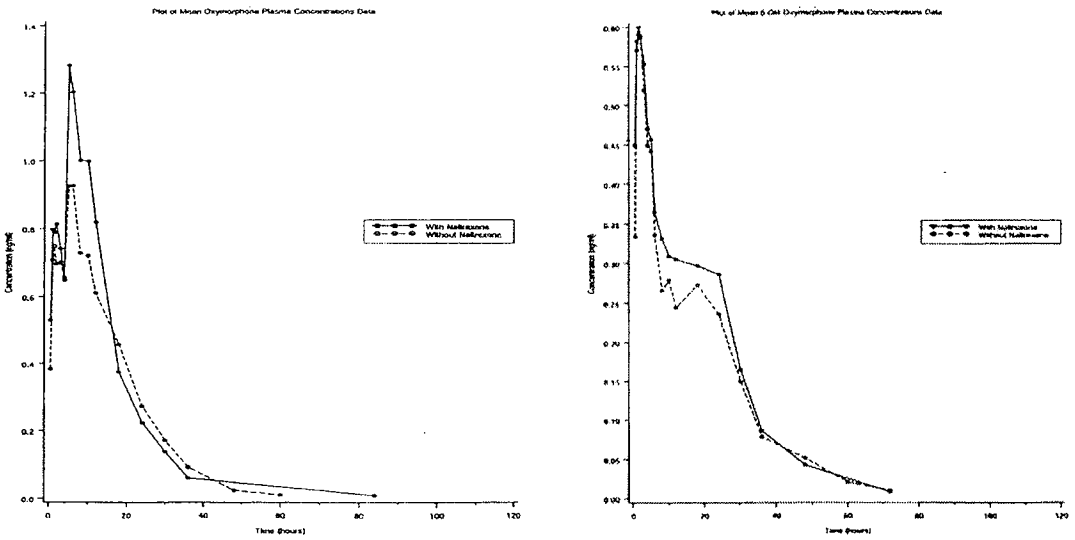
The creatinine – exposure relationship indicates that there are only small changes in the AUC for oxymorphone until the creatinine clearance approaches 50 mL/min, and that the most extreme changes occur when creatinine clearance falls to the level of severe impairment (<30 mL/min). There was no change in t1/2 of oxymorphone among all three groups.

To summarize, mean oxymorphone AUC was increased by 25, 57 and 65 % in mild, moderate, and severe renal impaired subjects, respectively. There was no change in t1/2 of oxymorphone among all three groups. Titration needs to be undertaken cautiously in subjects with moderate and severe renal impairment.

Is dosage adjustment needed due to concomitant administration of Naltrexone and other drugs?

The effect of naltrexone (1 x 50 mg single dose),-an antagonist to block the opioid effects of oxymorphone, on 20 mg oxymorphone ER (1 x 20 mg single dose) was assessed. The data indicated that naltrexone had a modest effect on the peak plasma concentration of oxymorphone (~38% increase) but did not appear to have a significant effect on either plasma AUC or the metabolism of oxymorphone.

The mean oxymorphone elimination half- life appeared to be slightly shorter in the presence of naltrexone (9.05 hours) compared to oxymorphone ER administered alone (13.79 hours). Naltrexone has a similar effect on morphine. In all, the use of naltrexone to block the opioid effects of oxymorphone ER is not likely to significantly affect the oxymorphone disposition.



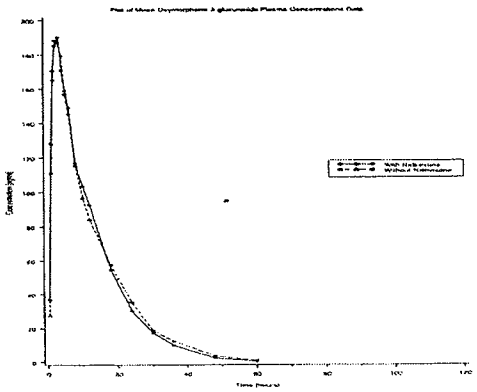


Table 6: Mean (SD) Plasma Pharmacokinetic Results

Pharmacokinetic Variable	EN3202 + Naltrexone	EN3202
Oxymorphone		
AUCT (ng•hr/mL)	17.75 (6.64)	16.39 (2.85)
AUC (ng•hr/mL)	19.69 (6.46)	19.73 (5.38)
C_{max} (ng/mL)	1.59 (0.84)	1.07 (0.23)
T_{max} (hr)*	5.0 (1.0–10)	5.0 (1.0–8.0)
λ_z (hr^{-1})	0.091 (0.038)	0.067 (0.026)
$T_{1/2}$ (hr)	9.05 (4.11)	13.79 (11.58)
6-OH-oxymorphone		
AUCT (ng•hr/mL)	11.05 (4.50)	10.19 (4.57)
AUC (ng•hr/mL)	14.35 (4.85)	13.17 (4.84)
C_{max} (ng/mL)	0.70 (0.24)	0.72 (0.27)
T_{max} (hr)*	1.5 (0.5–3.0)	2.0 (1.0–5.0)
λ_z (hr^{-1})	0.054 (0.025)	0.044 (0.016)
$T_{1/2}$ (hr)	16.39 (9.13)	17.60 (6.20)
Oxymorphone-3-glucuronide		
AUCT (ng•hr/mL)	2539.3 (547.4)	2559.3 (504.9)
AUC (ng•hr/mL)	2645.6 (550.7)	2691.0 (558.0)
C_{max} (ng/mL)	201.5 (45.8)	203.2 (50.0)
T_{max} (hr)*	2.5 (1.5–6.0)	2.0 (1.5–4.0)
λ_z (hr^{-1})	0.086 (0.019)	0.087 (0.023)
$T_{1/2}$ (hr)	8.50 (2.14)	8.58 (2.54)

Source: Appendix 2.19
*Median (range)

Table 7: Comparison of Plasma Pharmacokinetic Variables (geometric least square means and 90% confidence intervals)

Pharmacokinetic Variable	EN3202+ Naltrexone	EN3202	Ratio*	Upper 90% CI	Lower 90% CI
Oxymorphone					
ln-AUCT (ng•hr/mL)	16.74	16.15	1.04	0.81	1.32
ln-AUC (ng•hr/mL)	18.79	19.15	0.98	0.76	1.26
ln-C_{max} (ng/mL)	1.43	1.04	1.38	1.05	1.81
6-OH-oxymorphone					
ln-AUCT (ng•hr/mL)	10.20	9.43	1.08	0.70	1.67
ln-AUC (ng•hr/mL)	13.61	12.50	1.09	0.78	1.52
ln-C_{max} (ng/mL)	0.66	0.68	0.97	0.66	1.41
Oxymorphone-3-glucuronide					
ln-AUCT (ng•hr/mL)	2487.1	2511.8	0.99	0.79	1.24
ln-AUC (ng•hr/mL)	2594.4	2635.1	0.98	0.79	1.23
ln-C_{max} (ng/mL)	196.61	197.60	0.99	0.77	1.29

Source: Appendix 2.22
*geometric mean of test ÷ reference difference

In vitro studies in human recombinant human liver microsomes indicated that oxymorphone does not inhibit the activity of CYP450 1A2, 2C9, 2C19, 2D6, or 2E1. However, oxymorphone inhibited nifedipine dehydrogenation mediated by CYP450 3A4 at high concentrations (estimated IC_{50}=150 µM) but did not have an effect on 3A4-mediated hydroxylation of midazolam or testosterone. Since the inhibitory concentrations observed *in vitro* are on the order of 10,000 times higher than the expected concentrations in clinical use, the findings of this trial do not indicate any relevant level of risk for oxymorphone- inhibition of CYP450 3A4 or the other isozymes tested.

Additional *in vitro* studies in recombinant human liver hepatocyte indicated that oxymorphone did not produce any significant increase in the activity of CYP450 1A2, 2D6, or 2E1. However, CYP450 2C9 metabolite formation was observed to increase 1.2- and 1.3-fold after hepatocytes were incubated for 72 hours with oxymorphone at 10 or 30 µg/mL, respectively. Oxymorphone produced a statistically significant increase in the activity of CYP450 3A4 at 72 hours (3.3- fold) similar to that produced by dexamethasone and phenytoin (3.2- and 3.1-fold, respectively). Since the concentrations of oxymorphone shown to induce CYP450 2C9 and 3A4 activity *in vitro* are approximately 300- to 1,000- fold higher than the concentrations expected *in vivo*, the

significance of the findings in this study are uncertain. Currently, the Applicant stated that two clinical drug interaction studies are ongoing to investigate the effects of CYP450 3A4 and 2C9.

Are there any E-R relationships observed with IR tablets?

There is no exposure-response relationship information for IR tablets.

Are there any E-R relationships observed with ER tablets?

Simultaneous plasma concentration and pain intensity measurements were obtained from patients in Studies EN3202-016, EN3202-018, and EN3202-019 after receiving oxymorphone ER for periods up to 7 to 10 days. Pain intensity was measured on a 0-100 scale in Study EN3202-016 and on a 0-10 scale in Studies EN3202-018 and EN3202-019. The concentrations of oxymorphone and 6-OH-oxymorphone were measured at each time point. Plasma samples and pain intensity ratings were obtained just prior to dose administration ("trough") and 3 hours (Studies EN3202-018 and EN3202-019) or 4 hours (Study EN3202-016) after dose administration ("peak"). The relationship between the pain intensity score and plasma concentrations of oxymorphone and 6-OH-oxymorphone was explored using correlation techniques. Pearson's correlation statistic was calculated for concentration versus pain intensity with all concentrations combined and for the paired peak-trough differences. Each parameter was considered separately; Study EN3202-016 was analyzed alone while the results from Studies EN3202-018 and EN3202-019 were pooled. Data were available for a total of 55 patients in Study EN3202-016, and 68 patients in Studies EN3202-018 and EN3202-019. Pain intensity and oxymorphone plasma concentrations at trough and peak are summarized below:

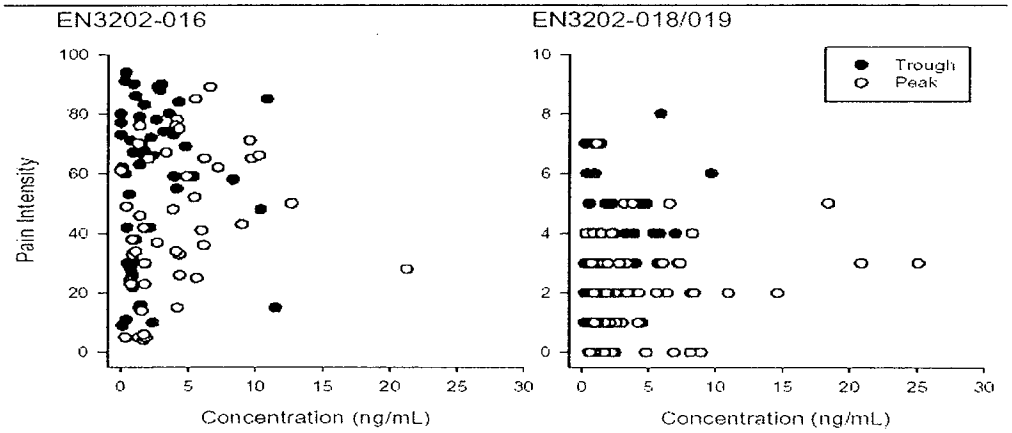
Mean (SD) Pain Intensity and Plasma Oxymorphone Concentration at Peak and Trough (Studies EN3202-016, EN3202-018, and EN3202-019)

	Trough	Peak
EN3202-016		
Pain Intensity		
N	52	45
Mean (SD)	57.33 (25.684)	43.98 (23.821)
Oxymorphone Concentration (ng/mL)		
N	52	53
Mean (SD)	2.40 (2.709)	4.42 (4.189)
EN3202-018/019		
Pain Intensity		
N	66	64
Mean (SD)	3.11 (1.993)	2.20 (1.565)
Oxymorphone Concentration (ng/mL)		
N	66	66
Mean (SD)	2.08 (2.045)	4.24 (4.793)

Source: Appendix II, Table 2.1

The Applicant reported that mean oxymorphone plasma concentrations increased by approximately 1.8-fold from trough to peak in Study EN3202-016 (patients with chronic low back pain) and mean pain intensity decreased by approximately 23%. The degree of change in both parameters was similar in the two cancer pain trials (EN3202-018 and EN3202-019); mean oxymorphone plasma concentrations increased approximately 2-fold from trough to peak and mean pain intensity decreased by about 29%.

Figure - Peak and Trough Pain Intensity versus Plasma Concentration
(Studies EN3202-016, EN3201-018, and EN3202-019)



The Applicant stated that results of the analyses revealed that there was no linear relationship between the oxymorphone plasma concentration and pain intensity. A weak but statistically significant association was observed between the 6-OH-oxymorphone concentration and pain intensity in Studies EN3202-018 and EN3202-019; however, the direction of the association was positive and therefore in the opposite direction from what would be expected. The Applicant stated that examination of the scatter plots indicates that the positive association is the result of a very small number of data points.

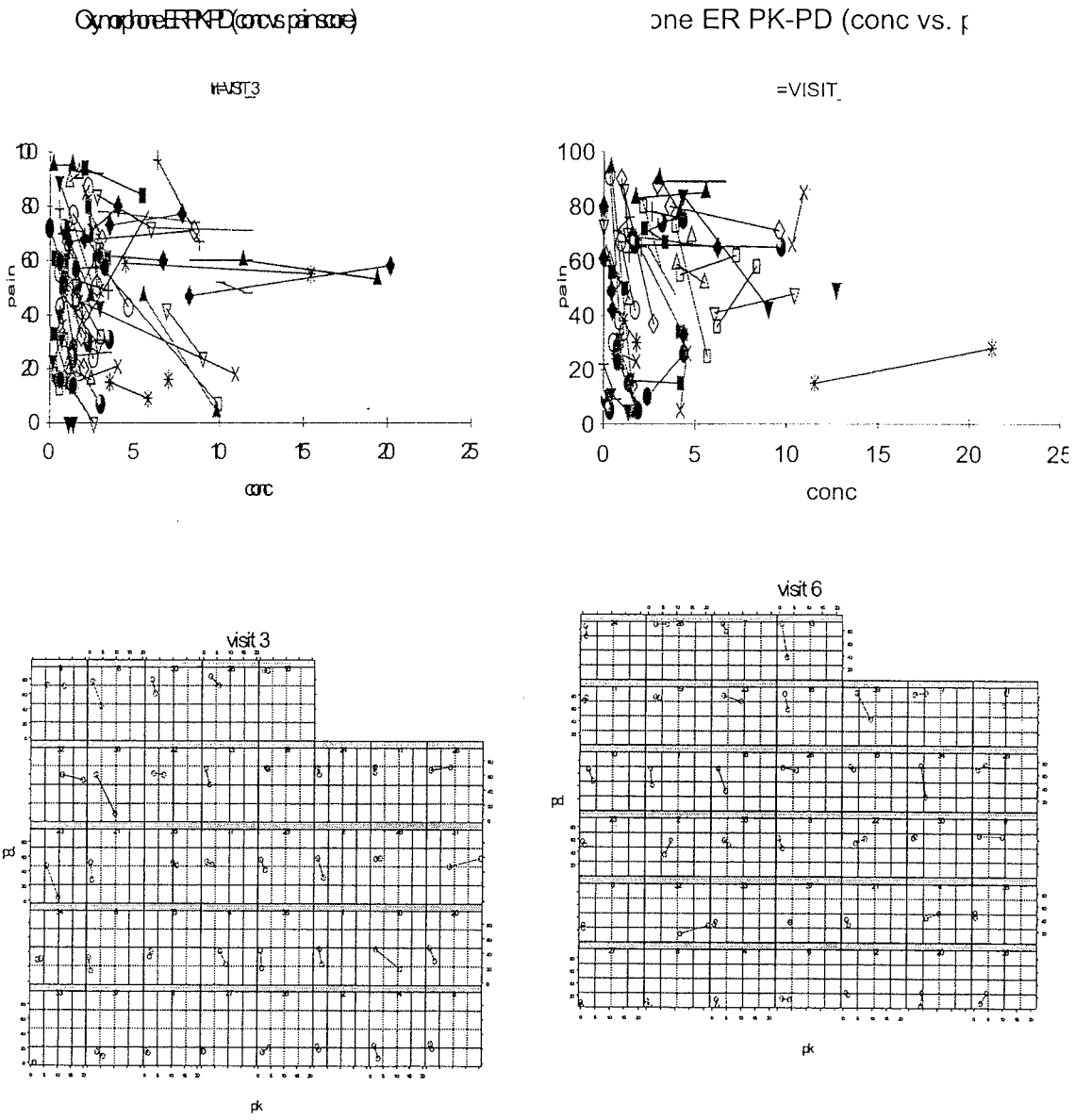
Additional analysis of Study EN3202-016 PK-PD relationship

The Applicant's data was further analyzed (Dr. He Sun, a pharmacometric scientist, and this reviewer). The following are the results from the linear mixed effect model analysis from all individual subjects:

1. As a control, a linear model was constructed. The model (with all subjects) predicted that a positive slope of 0.3699, indicating that a subject will feel more pain as the concentration increases. This conclusion is similar to that of the Applicant's conclusion.
2. A linear model for Visit 3 data indicated a positive slope, of 0.4168.
3. A linear model for Visit 6 data indicated a same trend - a positive slope of 0.3801.
4. If the individual variability is accounted with normal distribution assumption (linear model by individuals), a negative slope of 6.13 was observed. This indicates that one ng/mL concentration unit increase will result in a pain reduction of 6.13 units (100 point scale).
5. However, if one considers the log-normal distribution with random effect (linear mixed effect model), a negative slope of 1.26 was observed. This indicates that one ng/mL concentration unit increase will result in pain reduction of 1.26 units. For Visits 3 and 6, a negative slopes of 3.17 and 0.548 were observed.

In all, from an additional analysis, there is a reasonable assumption that there is some pain relief from oxymorphone. The results indicated that (from an arithmetic mean calculation) one concentration range (1 ng/mL) will decrease the pain score by 6.12 units (100 point scale). However, this finding needs to be further confirmed.

Figure – Linear model output



4.2 General Biopharmaceutics

What is the IR to-be-marketed tablet formulation?

Ingredient	Function	Tablet Composition (mg/tablet)	Exhibit Batch (kg/batch) Batch Size:	Proposed Commercial Production Batches (kg/batch) Batch Size:
Oxymorphone HCl, USP	Active Ingredient	5.00		
Lactose Monohydrate, NF	Filler			
Pregelatinized Starch, NF				
Magnesium Stearate, NF				
FD&C Blue #2 Aluminum Lake				
Total Theoretical Weight of final Drug Product		220.00	33.0	165.0

Ingredient	Function	Tablet Composition (mg/tablet)	Exhibit Batch (kg/batch) Batch Size:	Proposed Commercial Production Batches (kg/batch) Batch Size:
Oxymorphone HCl, USP	Active Ingredient	10.00		
Lactose Monohydrate, NF				
Pregelatinized Starch, NF				
Magnesium Stearate, NF				
D&C Red #30 Aluminum Lake				
Total Theoretical Weight of final Drug Product		220.00	33.0	165.0

What is the ER to-be-marketed tablet formulation?

Component	Oxymorphone ER 5 mg	10 mg	20 mg	40 mg
Oxymorphone HCl, USP	5.00	10.00	20.00	40.00
TIMERx-N Delivery System				
Silicified microcrystalline cellulose, NF				
Sodium stearyl fumarate, NF				
Total Weight				
Methylparaben				

[a] Equal to [redacted] of the tablet weight
[b] Ink for the printing of the tablet

What is the dissolution specification for IR tablet?

Oxymorphone IR Tablets, dissolution was changed from ——— of water to 900 mL of 0.1 N HCl using USP apparatus 2 at 50 rpm and 37° ± 0.5°C, where Q= ▬ at 30 minutes. The Applicant stated that the new dissolution parameters and specifications have been applied to on- going stability testing

Thus the Applicant's dissolution specifications for 5 and 10 mg oxymorphone HCl IR tablets dissolved in 0.1 N HCl :

Apparatus:	USP Apparatus 2 (paddles)
Media:	900 mL of 0.1 N HCl
Agitation Speed:	50 rpm
Temperature:	37±0.5°C
Sampling Time Points:	Profile: 5, 10, 20, and 30 minutes
Release Specifications	NLT ▬ (Q) in 30 minutes

What is the dissolution specification for ER tablets?

Dissolution profiles were determined for ▬ oxymorphone tablet batches (lots). The tablets were manufactured by ▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬ Novartis Consumer Health (Novartis). ▬ produced 10, 20, and 40 mg strength tablets, and Novartis produced 5, 10, 20, and 40 mg strength tablets.

The drug release rates were evaluated using USP Apparatus 2 (paddles) at 50 rpm in 50 mM phosphate buffer at pH 4.5.

Applicant's proposed dissolution specifications (ER Tablets in 900 mL of 50 mM Phosphate Buffer at pH 4.5):

Apparatus:	USP Apparatus 2 (paddles)	
Media:	900 mL of 50 mM phosphate buffer at pH 4.5	
Agitation Speed:	50 rpm	
Temperature:	37±0.5°C	
Sampling Time Points:	Release and Stability Testing: 1, 4, and 14 hours Profile: 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 14 hours	
Release Specifications	Time (Hr)	Amount Released (%)
	1	▬▬▬
	4	
	14	NLT ▬

Is there information on invitro-invivo correlation for ER tablets?

Dissolution and plasma concentration data from two studies, EN3202-001 and EN3202-011, were used to determine and validate *in vitro-in vivo* correlations (IVIVCs) for oxymorphone ER tablets.

The IVIVCs were computed based on tablets dissolved in two media, phosphate buffer at pH 4.5 and 0.1 N hydrochloric acid (HCl). The IVIVCs had internal and external validation mean prediction errors of <10% for Cmax and AUC 0-t .

IVIVCs were developed and validated using the following four oxymorphone ER formulations:

- the "slow-release" and "fast-release" 20 mg formulations that were used in Study EN3202-001 (EN3202-Slow and EN3202-Fast, respectively) and
- the 40 mg formulations manufactured by [redacted] and Novartis Consumer Health that were used in Study EN3202-011 (EN3202-[redacted] and EN3202-NOV, respectively). EN3202-Fast was the prototype formulation—initially, to be used in clinical trials, and later, to be marketed. This prototype was the basis for the formulations used to manufacture EN3202-[redacted] and EN3202-NOV tablets.

Table - Summary of Oxymorphone ER Formulations Used in IVIVC Computations:

	EN3202-Slow[a]	EN3202-Fast[a]	EN3202	EN3202-NOV[b]
Manufacturer	[redacted]			Novartis
Lot Number	9806706	980707	9905924[c]	310184[d]
Formulation	Tablet	Tablet	Tablet	Tablet
Oxymorphone HCl, USP (mg)	20.00	20.00	40.00	40.00
Total Weight (mg)	[redacted]			
Timerx-N Delivery System (mg)				

[a] "Slow" and "Fast" refer to the rate at which formulations released the active ingredient (based on the quantity of the control-releasing agent). These formulations were used in the pilot trials, EN3202-001 and EN3202-002.

[b] [redacted] and NOV (Novartis Consumer Health) refer to the manufacturers of the tablets used in the bioequivalence trials, Study EN3202-011 and -011A.

[c] Lot No. 9905924 tablets were used in the following clinical trials: EN3202-007, -008, -011, -011A, -016, -018, -019, -021, and -022.

[d] Lot No. 310184 tablets were used in the clinical trials, EN3202-011 and -011A.

EN3202-Slow tablets dissolved at a slower rate than the other three formulations regardless of the media used for dissolution. EN3202-Fast, EN3202-[redacted] and EN3202-NOV formulations dissolved at a very similar rate in both media, although overall, these formulations dissolved more quickly in 0.1 N HCl than in phosphate buffer at pH 4.5.

Based on similarities in the formulations and *in vitro* dissolution data, the EN3202-[redacted] and EN3202-NOV formulations were considered equivalent to EN3202-Fast.

In vivo absorption rates were determined using numerical deconvolution. The relationship between the cumulative percent dissolved *in vitro* and the cumulative percent absorbed *in*

vivo was determined using un-weighted linear least-squares regression. To obtain dissolution data points corresponding to the times at which plasma concentrations were measured, missing dissolution time points were imputed using linear extrapolation between the measured values.

Dissolution time points were not extrapolated beyond the last actual dissolution time point (12 or 14 hours), and plasma concentrations were not extrapolated. Comparison of the dissolution and deconvolution results indicated a rank order correlation between the percent dissolved and the percent absorbed.
The primary IVIVC (combined results of the slow and fast formulations) was highly significant for both dissolution media. The r^2 values were 0.966 and 0.962 for phosphate buffer at pH 4.5 and 0.1 N HCl, respectively. The slow and fast formulations had similar results. The regression slope for the primary IVIVC using phosphate buffer at pH 4.5 dissolution results (0.8919) was slightly higher than the slope using 0.1 N HCl dissolution results (0.8212). A near 1-to-1 relationship between *in vivo* absorption and *in vitro* dissolution was also demonstrated for the slow- and fast-release formulations in phosphate buffer at pH 4.5 and 0.1 N HCl.

Internal validation of the IVIVCs was conducted by using the IVIVCs developed from Study EN3202-001 to calculate predicted plasma concentrations. The predicted Cmax and AUC 0-t results were then compared to the observed ("actual") values. The actual Cmax and AUC 0-t values were computed from the mean plasma concentrations over the time interval corresponding to the prediction (i.e., for both EN3202-Slow and EN3202-Fast, 0 to 14 hours using phosphate buffer at pH 4.5 dissolution results and 0 to 12 hours using 0.1 N HCl dissolution results). The calculated pharmacokinetic parameters using phosphate buffer at pH 4.5 or 0.1 N HCl are summarized:

Table - IVIVC Internal Validation Results for Study EN3202-001 Using Phosphate Buffer at pH 4.5 Dissolution Results

Parameter	Formulation	Predicted	Actual	Prediction Error
Cmax (ng/mL)	EN3202-Slow (20 mg)	0.73	0.77	-4.15%
	EN3202-Fast (20 mg)	0.97	0.91	6.27%
Mean				1.06%
AUC_{0-t} (ng•hr/mL)	EN3202-Slow (20 mg)	8.47	8.27	2.40%
	EN3202-Fast (20 mg)	10.26	9.10	12.81%
Mean				7.61%

Cmax=Highest concentration observed during the predicted time interval; AUC_{0-t}=Area under the concentration-time curve from time 0 to the end of the predicted time interval using linear trapezoidal rule; Prediction Error=(Predicted - Actual)/ Actual × 100

Table - IVIVC Internal Validation Results for Study EN3202-001 Using 0.1 N HCl Dissolution Results

Parameter	Formulation	Predicted	Actual	Prediction Error
Cmax (ng/mL)	EN3202-Slow (20 mg)	0.82	0.77	7.15%
	EN3202-Fast (20 mg)	0.95	0.91	4.97%
Mean				6.06%
AUC_{0-t} (ng•hr/mL)	EN3202-Slow (20 mg)	7.73	6.91	11.86%
	EN3202-Fast (20 mg)	8.42	7.81	7.81%
Mean				9.83%

Cmax=Highest concentration observed during the predicted time interval; AUC_{0-t}=Area under the concentration-time curve from time 0 to the end of the predicted time interval using linear trapezoidal rule; Prediction Error=(Predicted - Actual)/ Actual × 100

External validation of the IVIVCs was conducted by using the IVIVCs developed in Study EN3202-001 to predict the Cmax and AUC 0-t (0 to 12 hours using either dissolution medium) for the EN3202[redacted] and EN3202-NOV formulations used in Study EN3202-011. The calculated pharmacokinetic parameters using phosphate buffer at ph 4.5 or 0.1 N HCl are summarized :

Table - IVIVC External Validation Results for Study EN3202-001 Using Phosphate Buffer at pH 4.5 Dissolution Results:

Parameter	Formulation	Predicted	Actual	Prediction Error
Cmax (ng/mL)	EN3202-NOV (40 mg)	2.11	2.29	-7.90%
	EN3202[redacted] 40 mg)	2.08	2.19	-5.04%
Mean				-6.47%
AUC_{0-t} (ng•hr/mL)	EN3202-NOV (40 mg)	19.48	19.69	-1.06
	EN3202-[redacted] (40 mg)	19.40	19.52	-0.61%
Mean				-0.83%

Cmax=Highest concentration observed during the predicted time interval; AUC_{0-t}=Area under the concentration-time curve from time 0 to the end of the predicted time interval using linear trapezoidal rule; Prediction Error=(Predicted - Actual)/ Actual × 100

Table - IVIVC External Validation Results for Study EN3202-001 Using 0.1 N HCl Dissolution Results:

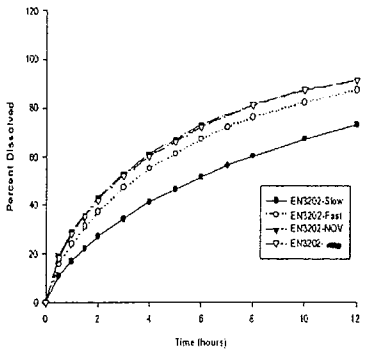
Parameter	Formulation	Predicted	Actual	Prediction Error
Cmax (ng/mL)	EN3202-NOV (40 mg)	2.09	2.29	-8.63%
	EN3202-[redacted](40 mg)	1.98	2.19	-9.56%
Mean				-9.10%
AUC_{0-t} (ng•hr/mL)	EN3202-NOV (40 mg)	19.18	19.69	-2.57%
	EN3202-[redacted](40 mg)	18.13	19.52	-7.11%
Mean				-4.84%

Cmax=Highest concentration observed during the predicted time interval; AUC_{0-t}=Area under the concentration-time curve from time 0 to the end of the predicted time interval using linear trapezoidal rule; Prediction Error=(Predicted - Actual)/ Actual × 100

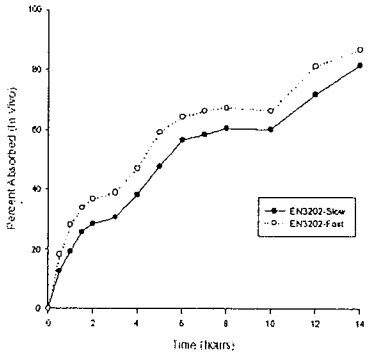
In all, highly significant IVIVCs were developed for oxymorphone ER on the basis of plasma concentration data from Study EN3202-001 and two different dissolution media (phosphate buffer at pH 4.5 and in 0.1 N HCl). Study EN3202-001 included one fast-

releasing formulation (EN3202-Fast) and one slower-releasing formulation (EN3202-Slow) of oxymorphone ER. These two oxymorphone ER formulations demonstrated a clear rank order correlation for both *in vitro* percent dissolved in phosphate buffer at pH 4.5 or 0.1 N HCl and *in vivo* percent absorbed. Results of the internal and external validations demonstrated that a Level A correlation was obtained and the IVIVCs can be used to predict the observed Cmax and AUC 0-t values with a prediction error ≤10% on average and ≤15% prediction error for any individual observation.

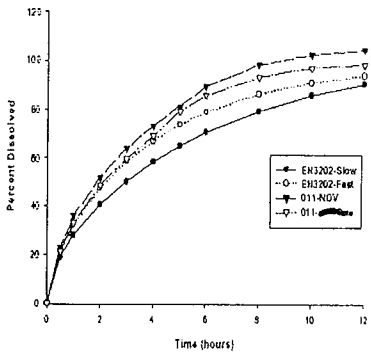
Mean Dissolution in Phosphate Buffer at pH 4.5 (Data Extrapolated to Match Plasma Concentration Time Points)



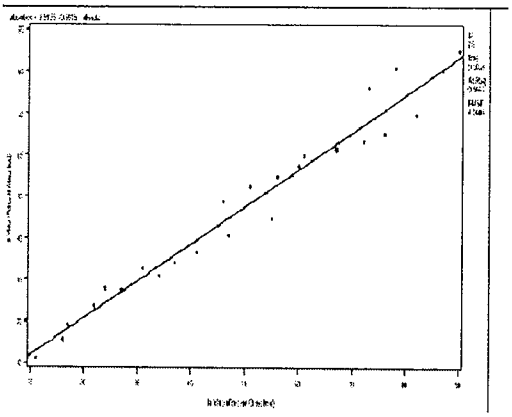
Study EN3202-001: Mean Percent of Dose Absorbed Determined by Numerical Deconvolution



Mean Dissolution in 0.1 N HCl (Data Extrapolated to Match Plasma Concentration Time Points)



Primary *In Vitro-In Vivo* Correlation Based on Combined Slow- and Fast-Release Oxymorphone ER Formulations (Study EN3202-001) Using Phosphate Buffer at pH 4.5 Dissolution Results



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Primary *In Vitro-In Vivo* Correlation Based on Combined Slow- and Fast-Release Oxymorphone ER Formulations (Study EN3202-001) Using 0.1 N HCl Dissolution Results

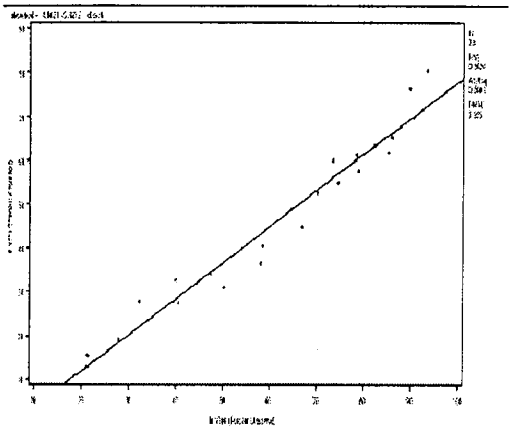


Figure 6. Internal Validation: Actual and Predicted Plasma Oxymorphone Concentrations Using Phosphate Buffer at pH 4.5 Dissolution Results

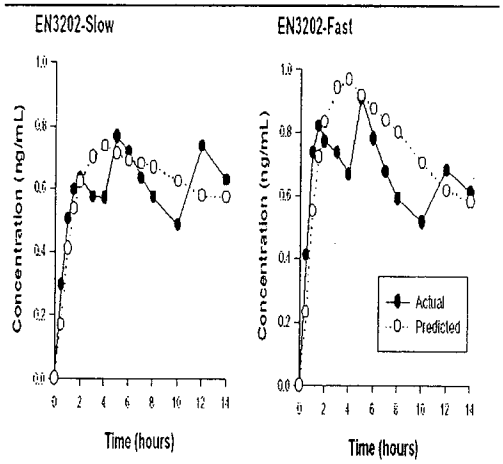


Figure 7 Internal Validation: Actual and Predicted Plasma Oxymorphone Concentrations Using 0.1 N HCl Dissolution Results

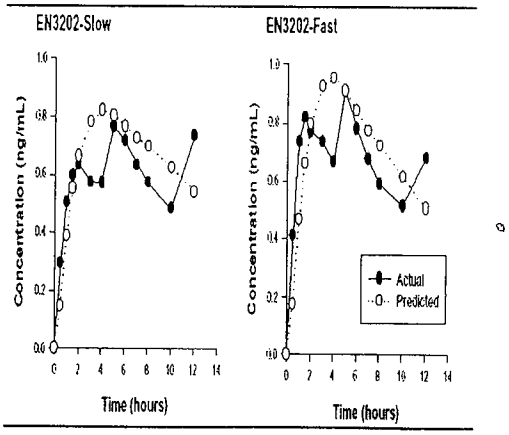


Figure 8. External Validation: Actual and Predicted Plasma Oxymorphone Concentrations Using Phosphate Buffer at pH 4.5 Dissolution Results

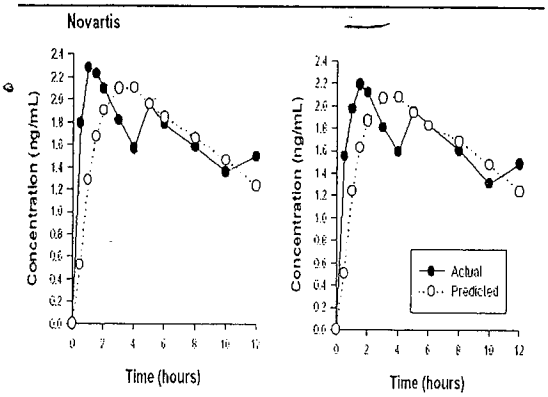
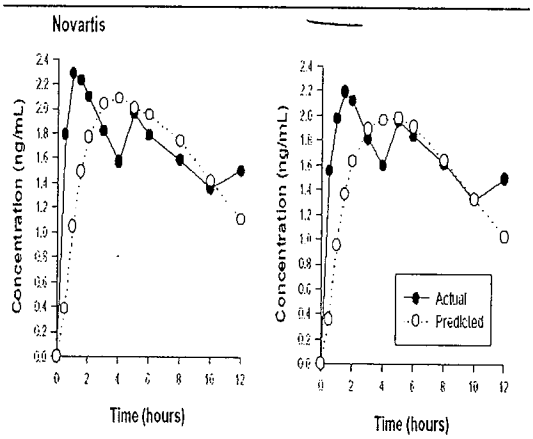


Figure 9 External Validation: Actual and Predicted Plasma Oxymorphone Concentrations Using 0.1 N HCl Dissolution Results



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4.3 Assays

The plasma and urine concentrations of oxymorphone and oxymorphone metabolites reported in this application were determined using two different analytical methods, gas chromatographic mass spectrometry (GC/MS) or liquid chromatographic/mass spectrometry/mass spectrometry (LC/MS/MS). The GC/MS method for plasma was developed at [redacted] and the LC/MS/MS methods for plasma and urine were developed at [redacted]. Brief descriptions of each method are provided in this section. A summary of the methods and the studies in which they were used is provided:

Study No.	Method No.	Method	Type	LLQ-ULQ (ng/mL)[a] OXM	6-OH-OXM	OXM-3-G	Lab[b]
EN3202-004	[redacted]	LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	[redacted]
		LC/MS/MS	plasma	----	----	5 – 250	
		LC/MS/MS	urine	2.0 – 400	2.0 – 400	----	
		LC/MS/MS	urine	1.0 - 200	1.0 - 200	----	
		LC/MS/MS	urine	----	----	10 – 2000	
EN3202-005		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
		LC/MS/MS	plasma	----	----	5 – 250	
		LC/MS/MS	urine	2.0 – 400	2.0 – 400	----	
		LC/MS/MS	urine	1.0 - 200	1.0 - 200	----	
		LC/MS/MS	urine	----	----	10 – 2000	
EN3202-006		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
		LC/MS/MS	plasma	----	----	5 – 250	
		LC/MS/MS	urine	1.0 - 200	1.0 - 200	----	
		LC/MS/MS	urine	----	----	10 – 2000	
EN3202-007		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
		LC/MS/MS	plasma	----	----	5 – 250	
EN3202-008		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
		LC/MS/MS	plasma	----	----	5 – 250	
		LC/MS/MS	urine	1.0 - 200	1.0 - 200	----	
		LC/MS/MS	urine	----	----	10 – 2000	
EN3202-009		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
EN3202-010		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
		LC/MS/MS	plasma	----	----	5 – 250	
		LC/MS/MS	urine	1.0 - 200	1.0 - 200	----	
		LC/MS/MS	urine	----	----	10 – 2000	
EN3203-001		GC/MS	plasma	0.052 – 5.2	----	----	
EN3203-002		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
		LC/MS/MS	plasma	----	----	5 – 250	
EN3203-006		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
		LC/MS/MS	plasma	----	----	5 – 250	
EN3203-007		LC/MS/MS	plasma	0.1 – 20	0.1 – 20	----	
		LC/MS/MS	plasma	----	----	5 – 250	

[a] LLQ is the lower limit of quantitation; ULQ is the upper limit of quantitation.
[b] [redacted]

OXM=Oxymorphone; 6-OH-OXM=6-OH-oxymorphone; OXM-3-G=Oxymorphone-3-glucuronide

5 Labeling

The Applicant's proposed package inserts are attached below. The Labeling review is conducted under a separate cover for both IR and ER tablete.

36 Page(s) Withheld

_____ Trade Secret / Confidential

_X_ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

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David Lee
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