CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-610

21-611

MEDICAL REVIEW

2nd Cycle

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

DEPUTY DIVISION DIRECTOR APPROVAL MEMO

DATE:	June 22, 2006
SUBMISSION DATE:	December 22, 2005
DRUG:	Oxymorphone Hydrochloride Extended-Release Tablets Oxymorphone Hydrochloride Immediate-Release Tablets
TRADENAME:	OPANA ER OPANA
NDA:	21-610, 505 (b)(1), Response to Approvable Action 21-611
SPONSOR:	Endo Pharmaceuticals
DOSAGE FORM:	Oral
DOSAGE STRENGTHS:	5, 10, 20, and 40 mg (Extended-Release) 5 and 10 mg (Immediate-Release)
INDICATIONS:	The management of moderate to severe pain requiring around-the-clock opioid therapy for an extended period of time (Extended-Release) The management of moderate to severe acute pain (Immediate-Release)

RECOMMENDED ACTION: Approval of NDA 21-610 oxymorphone hydrochloride extended-release tablets and approval of NDA 21-611 oxymorphone hydrochloride immediate-release tablets.

SUMMARY OF FINDINGS

1. There is evidence of efficacy of oxymorphone extended-release tablets dosed every 12 hours when titrated to efficacy and tolerability in chronic pain requiring around-the-clock opioids for an extended period of time. The safety finding of numerous reports of hypoxia requiring treatment with an opioid antagonist from a study of oxymorphone ER

in the postoperative period indicates that this formulation of oxymorphone is not appropriate for the postoperative setting.

2. There is evidence of efficacy for oxymorphone immediate-release tablets dosed as 10 mg and 20 mg every four to six hours in acute pain. A dose of 30 mg every six to eight hours in the postoperative setting in opioid naïve patients did not provide any greater analgesia than the 20 mg dose but did yield an unacceptably high rate of hypoxia requiring treatment with an opioid antagonist. This finding indicates that maximum initial dose in this setting should be 20 mg.

3. Elderly patients are most susceptible to hypoxia in the postoperative setting indicating the need for careful titration in this population.

4. Equianalgesic potency is unclear. An attempt to determine the relative analgesic potency of oxymorphone extended-release tablets compared to modified-release oxycodone tablets and modified-release morphine tablets was unsuccessful. Guidance for the conversion of opioid tolerant patients from oxycodone, morphine, fentanyl, and methadone to oxymorphone ER that will be included in the package insert has been informed by conversion ratios for each drug used during a clinical trial, but this cannot be considered adequate evidence of equianalgesic potency.

5. Oxymorphone ER and oxymorphone IR are contraindicated in moderate and severe hepatic impairment due to increased bioavailability of 3.7-fold and 12.2-fold, respectively.

6. An *in vivo* study of the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of OPANA ER in healthy, fasted volunteers found a highly variable effect on Cmax with concomitant administration of alcohol and OPANA ER. The change in Cmax ranged from a decrease of 50% to an increase of 270% across all conditions studied. As the *in vitro* study of oxymorphone ER with alcohol (5%, 20%, and 40%) did not demonstrate an increased rate of release in oxymorphone, the *in vivo* effect may not be due to dose dumping but may instead be due to enhanced absorption of oxymorphone. Therefore alcohol should not be ingested in patients taking either oxymorphone ER or oxymorphone IR.

7. After oral dosing with a single dose of 40 mg in fasted subjects, the mean peak oxymorphone plasma level is 2.4 ng/mL and the median T_{max} is 2 hours. The Applicant has recommended that oxymorphone ER and oxymorphone IR be taken on an empty stomach.

8. A Risk Minimization Program has been prepared by the Applicant to address concerns associated with modified-release opioids.

BACKGROUND

Oxymorphone immediate-release tablets 2, 5, and 10 mg were first approved by the FDA (NDA-11-737) in 1959 and marketed under the trade name Numorphan. The Applicant reports that the oral tablets were removed from the market in 1979, for commercial reasons. Oxymorphone injectable, 1 mg/ml, for intramuscular and subcutaneous administration (NDA 11-707) and oxymorphone rectal suppository, 2 mg and 5 mg, (NDA 11-707 and NDA 11-738) were approved by the Agency in 1959. Both products are currently marketed in the U.S. Studies were performed under IND 56,919 (oxymorphone ER) and IND 58,602 (oxymorphone IR).

This submission represents a complete response to an Approvable action dated October 15, 2003 for NDA 21-610 oxymorphone hydrochloride extended-release tablets (oxymorphone ER) 5, 10, 20, and 40 mg tablets and NDA 21-611 oxymorphone hydrochloride immediate-release (oxymorphone IR) 5 and 10 mg tablets. The original NDAs were submitted on December 19, 2002.

An approvable action was issued because the two efficacy studies submitted to the initial application were not considered successful in providing support of efficacy (EN3202-015 and EN3202-025). One study of oxymorphone ER in the immediate postoperative period submitted in the original application (EN3202-012) did show evidence of analgesic efficacy but with an unacceptable rate of hypoxia.

In this resubmission, the results of two new 12-week clinical trials (EN3202-031 and EN 3202-032) have been submitted in support of efficacy for oxymorphone ER with support from an 18-day placebo-controlled efficacy study (EN3202-016) submitted in the initial application.

The results of one new multiple-dose study in acute postoperative pain (EN3203-009) has been submitted in support of efficacy for oxymorphone IR. One multiple-dose study submitted with the initial application (EN3203-004) and one single-dose study (EN3203-005) provided evidence of efficacy for oxymorphone IR. However, these studies failed to provide adequate support for the proposed dosing regimen of every six [redacted] hours.

Support for the safety side of the risk benefit analysis is provided by the original safety database with patients who had been exposed to oxymorphone ER and oxymorphone IR plus additional data from the two new studies efficacy trials of oxymorphone ER with oxymorphone IR as rescue medication (EN3202-031, EN3202-032) and additional data from two open-label extension studies ongoing at the time of the safety update from the original submission (EN3202-021 and EN3202-22) and two new open-label safety studies (EN3202-028 and EN3202-029). Additional safety information in the ISS includes data from two efficacy studies of the oxymorphone IR (EN3203-008 and EN3203-009).

Two trade names have been proposed by the Applicant. During the first review cycle, the Office of Drug Safety had raised concerns about the name OPANA and confusion with tincture of opium, but given the differences in dosage form, this concern has been dismissed by the Office of Drug Safety and the division.

CMC

Dr. Jila Boal reviewed the CMC material submitted in support of this application and has recommended approval from the product quality standpoint. The primary means of controlling the drug release for oxymorphone ER is via the excipient TIMERx-N®, a hydrophilic matrix and [redacted]. Xanthum gum in the formulation hydrates when exposed to water forming a polysaccharide gel network which enables additional water to diffuse into the TIMERx-N granulation. Less soluble locust bean gum then begins to hydrate and form a cohesive gel matrix with the xanthum gum. Drug release the occurs primarily by diffusion [redacted].

There were numerous CMC deficiencies identified in the original NDA submission. As the oxymorphone ER formulation contains a relatively small amount of drug substance, the potential for agglomeration or segregation within the bulk blended drug product required appropriate sampling for homogeneity testing . Particle size specifications based on [redacted] were established for the drug substance. A [redacted] specification for the particle size distribution of the TIMERx-N particle size was set. The Applicant also provided [redacted]

[redacted]

[redacted]. Acceptance criteria for degradation products were revised according to ICH Q3 B recommendations. The stability data showed that the [redacted] total degradation products remained within specifications beyond [redacted] months supporting an expiration dating period of 36 months. The drug substance specifications have been revised according to ICH Q3A. The [redacted] present as process impurities from the synthesis of the drug substance are controlled [redacted] on an interim basis and will be tightened further based on action by the DMF vendor. Dr. Boal concludes that the Applicant has provided an adequate response to the deficiencies identified in the NDA action letter dated October, 15, 2003.

PHARMACOLOGY AND TOXICOLOGY

Dr. Mamata De performed the review of the nonclinical pharmacology and toxicology data. For this resubmission, carcinogenicity studies in the rat and mouse were performed and found to be negative for drug-related neoplasms. The mechanism of oxymorphone-induced positive findings in the *in vivo* micronucleus assay was studied by the applicant and adequate data was provided suggesting that the increase in the incidence of micronuclei formation is indirectly related to activation of opioid receptors. See Dr. De's review for greater detail. The applicant elected to reduce the levels [redacted] to below the ICH qualification threshold rather than qualify them at higher levels. The applicant provided *in vitro* genetic toxicology screens for [redacted]. The [redacted] were positive in the in vitro chromosome

aberration assay. The division has an agreement in place with the DMF holder for the reduction of the levels of these impurities over time. The [redacted] was negative in both genetic toxicology studies and is considered qualified.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

No deficiencies were cited in the Clinical Pharmacology and Biopharmaceutics Review of the original NDA by Dr. David Lee. In the current submission, the applicant submitted the results of in vitro and in vivo alcohol oxymorphone ER interaction results, food effect study results, oxymorphone IR single- and multiple-dose information and results from a simulation of 4-hour and 8-houroxymrphone IR multiple dosing regimens based on a single-dose oxymorphone 6-hour pharmacokinetic information.

The *in vitro* studies demonstrated that when the oxymorphone ER 40 mg formulation was mixed with 500 mL of 0.1N HCl solutions containing ethanol (4%, 20%, and 40%) there was no increase in release of oxymorphone from the formulation. The release rates actually correlated inversely with the amount of ethanol.

An *in vivo* study examined the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of oxymorphone ER in healthy, fasted volunteers. The results showed that the oxymorphone mean AUC was 13% higher (not statistically significant) after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of oxymorphone ER and ethanol (240 mL of 20% or 4% ethanol).

There was a highly variable effect on Cmax with concomitant administration of alcohol and oxymorphone ER. The change in Cmax ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following concomitant administration of 240 mL of 40% ethanol the Cmax increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the Cmax increased on average by 31% and up to 260% in individual subjects. Following the concomitant administration of 240 mL of 4 % ethanol, the Cmax increased 7% on average and by as much as 110% for individual subjects. After oral dosing with a single dose of 40 mg in fasted subjects, the mean peak oxymorphone plasma level is 2.4 ng/mL and the median T_{max} is 2 hours. Following co-administration of oxymorphone ER and alcohol (240 mL of 40% ethanol) in fasted subjects, the mean peak oxymorphone level is 3.9 ng/mL and the median T_{max} is 1.5 hours (range 0.75 – 6 hours).

Alcohol interaction studies were not performed with oxymorphone IR. As the in vitro study of oxymorphone ER with alcohol failed to demonstrate an increased rate of release in oxymorphone, the in vivo effect may not be due to dose dumping and may be due to enhanced absorption of oxymorphone. Therefore alcohol should not be ingested in patients taking either oxymorphone ER or oxymorphone IR.

The results of the food effect study submitted in this response is similar to the data submitted in the original applications. Two studies found that after the administration of oxymorphone ER, the C_{max} was increased by approximately 50% in fed subjects compared to fasted subjects. The AUC was unchanged in one study and increased by approximately 18% in the other study in fed

subjects. After oral dosing with a single dose of 40 mg, a peak oxymorphone plasma level of 2.8 ng/ml is achieved at 1.0 hour in fasted subjects and a peak of 4.25 ng/ml is achieved at 2.0 hours in fed subjects and that beyond the 12 hour time point, there is very little difference in the curves. The applicant recommends that oxymorphone ER be dosed at least one hour prior to or two hours after eating. For oxymorphone IR, food increased both oxymorphone Cmax and AUC by 38%.

Oxymorphone IR 5, 10, and 20 mg exhibited dose linearity after single and multiple dosing every six hours for four days. Simulations of four and eight-hour dosing regimen were created by the sponsor and found to be underestimates of the average steady-state concentrations by 14-25%.

The general pharmacokinetic parameters of oxymorphone ER are presented in the following table taken from the proposed package insert.

Table 1: Pharmacokinetic parameters of oxymorphone ER after five days of every 12 hour dosing.

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{½}$ (hr)
Single Dose	5 mg	0.27±0.13	4.54±2.04	11.30±10.81
	10 mg	0.65±0.29	8.94±4.16	9.83±5.68
	20 mg	1.21±0.77	17.81±7.22	9.89±3.21
	40 mg	2.59±1.65	37.90±16.20	9.35±2.94
Multiple Dose	5 mg	0.70±0.55	5.60±3.87	NA
	10 mg	1.24±0.56	9.77±3.52	NA
	20 mg	2.54±1.35	19.28±8.32	NA
	40 mg	4.47±1.91	36.98±13.53	NA

CLINICAL STUDIES AND STATISTICAL ANALYSIS

Dr. Christina Fang performed the clinical review and Dr. Dionne Price performed the statistical review.

Oxymorphone ER

Overview of Original Application – Oxymorphone ER

In the initial application, the Applicant submitted the results of four placebo-controlled studies in support of efficacy, safety, and dosing recommendations for oxymorphone ER. The results of three open-label or active-controlled trials were submitted in support of safety and to establish relative potency with approved modified-release opioids. The results from three open-label studies were submitted in support of safety.

EN3202-012 was a double-blind, parallel group, placebo-controlled, multiple-dose study of oxymorphone ER intended to evaluate the efficacy and safety of a 20 mg dose of oxymorphone ER, to characterize the analgesic onset and duration of oxymorphone ER effect in a single-dose paradigm, and to evaluate the opioid dose-sparing effects of oxymorphone ER after multiple dosing in patients with acute pain following orthopedic surgery. While there was evidence of

efficacy, many patients failed to achieve meaningful pain relief during the first 12 hours. Furthermore, there was a disproportionate number of subjects requiring treatment with naloxone raising concerns about the safety of oxymorphone ER in the postoperative setting.

EN3202-015 was a 4-week, double-blind, parallel group, placebo- and active-controlled, multiple-dose study of oxymorphone ER intended to support the efficacy and safety of two doses of oxymorphone ER (20 and 40 mg) compared to placebo and OxyContin, in patients with osteoarthritis of the knee and/or hip. The primary efficacy endpoint, change from baseline in Arthritis PI by VAS, failed to provide evidence of efficacy for the two doses of oxymorphone ER studied when a conservative imputation method was used to impute missing data.

EN3202-016 was a double-blind, placebo- and active-controlled, randomized withdrawal study of oxymorphone ER. After 7-10 days of double-blind titration with oxymorphone ER or OxyContin to reach a stable dose that provided satisfactory pain relief, patients were randomized to continue with current treatment or receive placebo for 18 days. Efficacy was demonstrated by the change from baseline to the 4-hour post-dose VAS PI on Day 18, which was statistically significantly better for the oxymorphone ER group compared with placebo.

EN3202-025 was a double-blind, parallel-group, placebo-controlled study of 10, 40, and 50 mg doses of oxymorphone ER The purpose of this 2-week, dose-ranging study was to identify the minimum effective dose and maximum tolerable dose in patients with moderate to severe pain due to osteoarthritis. The primary efficacy endpoint, change from baseline in Arthritis PI by VAS, failed to provide evidence of efficacy when an appropriate method of imputation was used, as for study 015.

EN3202-017 was an open-label, crossover study of oxymorphone ER, OxyContin, and MS Contin in patients with cancer pain to determine the relative potency of oxymorphone compared to oxycodone and morphine. The study design was unable to achieve the study's objective due at least in part to the open-label design, allowance for dose adjustments and rescue medication, and limited dosing flexibility of the oxymorphone ER (20 mg).

EN3202-018 was a randomized, double-blind, crossover study intended to demonstrate analgesic equivalence between oxymorphone ER and MS Contin and determine the equianalgesic dose ratio between these two products. A valid dose ratio could not be calculated as there was a statistically significant sequence effect.

EN3202-019 was a randomized, double-blind, crossover study intended to demonstrate analgesic equivalence between oxymorphone ER and OxyContin and the equianalgesic dose ratio between these two products. An equianalgesic was not definitively established.

Long-term safety data was obtained from the following three studies.
EN3202-020 was an open-label study enrolling patients who completed or discontinued early from studies EN3202-015 and EN3202-017 permitting continuation of treatment with study drug for up to two years.

EN3202-021 was an open-label study enrolling patients who completed or discontinued early from studies EN3202- 016 and EN3202-019 permitting continuation of treatment with study from for up to one year.

EN3202-022 was an open-label study enrolling patients who completed or discontinued early from study EN3202- 018 permitting continuation of treatment with study for up to one year.

NEW EFFICACY STUDIES – OXYMORPHONE ER

The current submission consists of new data from two completed adequate and well controlled efficacy studies, EN3202-031 (031), EN3202-032 (032), safety data from two completed open-label safety studies, EN3202-028 and EN3202-029, and safety data from two ongoing open-label studies, EN3202-021 and EN3202-022.

Study EN3202-031

Study EN3202-031 was a multi-center, double-blind, placebo-controlled, randomized withdrawal design study with a 28-day open-label titration period followed by a 12-week double-blind treatment period. The study was intended to support efficacy and safety of oxymorphone ER in opioid-naïve patients with chronic low back pain (LBP). It was also intended to define a safe dose titration regimen and dose range.

The study was to have enrolled male and non-pregnant female patients over 18 years of age with a history of moderate to severe chronic non-neuropathic LBP daily for at least several hours per day for a minimum of three months prior to screening. Patients were to have been on stable adjunct therapy (e.g., physical therapy, biofeedback therapy, acupuncture therapy, or herbal remedies) for back pain and were to have been opioid naïve, defined as on no more than an equianalgesic equivalent of oxycodone of 5 mg/day over the 14 days prior to screening. Patients were to have an initial pain score of at least 50 mm on a 100-mm VAS scale at baseline.

Patients were to undergo open-label titration on oxymorphone ER beginning with 5 mg every 12 hours for two days and then titrating by increments of 5-10 mg every 12 hours every 3-7 days until stabilization, defined as a pain score of less than 40 mm on same dose for three of five consecutive days. Patients who successfully reached a minimum dose of 10 mg every 12 hours were then to have been randomized into the double-blind treatment period, continuing on their stabilized dose or placebo. Rescue medication was not to have been permitted during the open-label titration. During the first four days of the double-blind period, rescue was to have been permitted, oxymorphone IR 5 mg every 4 to 6 hours, but was to then have been limited to no more than two doses per day for the remainder of the 12-week double-blind period.

The primary efficacy endpoint was to have been the change in average pain intensity from baseline to final visit, by VAS over the prior 24 hours, Secondary endpoints were to have included the change from baseline to final visit in patient's global assessment of pain medication and physician's global assessment of pain medication, an evaluation of compliance and study medication usage, and time to discontinuation due to lack of efficacy. Safety monitoring was to include adverse events, vital signs at most clinic visits, the Adjective Rating Scale for Withdrawal (ARS) and the Clinical Opiate Withdrawal Scale (COWS). Adverse events were to have been coded using the MedDRA system.

Missing efficacy values were to have been imputed using screening PI (worst case) carried forward for dropouts due to an AE, baseline PI (best case) carried forward for dropouts due to opioid withdrawal in the placebo group, and last observation carried forward for dropouts due to all other reasons.

The analysis population was to have been all patients who received at least one dose of study medication. The Applicant created a modified intent-to-treat population based on the exclusion of 14 patients, one who failed to sign the HIPAA as required, and 13 patients who failed to reach the prespecified minimum dose of oxymorphone ER 10 mg every 12 hours but were randomized into the second period of the study.

Results

A total of 326 patients entered open-label titration. One patient never received study drug. Of the remaining 325 patients, only 205 successfully completed the open-label titration period (including the 12 patients who did not reach the minimum oxycodone dose). The most common reason for discontinuation during the open-label titration was adverse events, accounting for 59 patients (18%). The next most common reason was failure to meet the titration-stabilization criteria for 23 patients (7%), consent was withdrawn by another eight patients, and "investigator opinion accounted for another five patients. The reason for discontinuation was further investigated by Dr. Fang for those patients who discontinued due to withdrawn consent, Investigator Opinion, Other, and Sponsor Request. None of these patients' reason for withdrawal included either lack of efficacy or adverse events.

Table 2. Patient Disposition During the Open-Label Titration Period: Number (%) of Patients

Patient Disposition	Oxymorphone ER
Entered Open-Label Titration Period	326 (100.0)
All Treated (Open-Label Titration Period)[a]	325 (99.7)
Not Treated[b]	1 (0.3)
Completed Open-Label Titration Period	205 (62.9)
Discontinued in Open-Label Titration Period	120 (36.8)
Adverse Event	59 (18.1)
AE not due to opioid withdrawal	59 (18.1)
Opioid withdrawal-AE	0
Patient did not meet Titration-Stabilization criteria	23 (7.1)
Withdrew Consent	14 (4.3)
Lost to Follow-up	8 (2.5)
Investigator Opinion	5 (1.5)
Protocol Violation	5 (1.5)
>3 days of <80% compliance with study medication	1 (0.3)
Other	4 (1.2)
Lack of Efficacy	4 (1.2)
Sponsor Request	2 (0.6)
Randomized and Entered Double-Blind Treatment Period	205 (62.9)

a All patients who received at least one dose of the Open-Label Titration medication.
b Patient 031-021 was not treated according to Drug Accountability data.
Note: For Patient 036-014, the reason for discontinuation was coded to AE, instead of Protocol Violation, to be consistent with the Adverse Event Case Report Form

Source: Applicant's Table 3 Study Report en3202031.pdf

During the double-blind period, there were further early discontinuations. Table 3 taken from Dr. Fang's review shows that only 68% of patients on oxymorphone ER completed the double-blind period compared to 47% of the patients randomized to placebo. Given the limited rescue medication available, it is not surprising that the most common reason for dropout in the placebo patients was lack of efficacy (35%). It is surprising that lack of efficacy was also the most common reason for early discontinuation in the double-blind period for the oxymorphone ER group (11%). Adverse events was next most common for both treatment groups followed by withdrawn consent. Further evaluation of the CRFs of patients who withdrew consent by Dr. Fang did not find these were due to adverse events.

Table 3 (Dr. Fang's Table 31-3) Patient disposition during the double-blind treatment period – number (%) of patients

Patient Disposition	Oxymorphone ER	Placebo	Overall
Randomized and entered double-blind treatment period	105 (100.0)	100 (100.0)	205 (100.0)
All treated patients (≥1 dose of double-blind treatment)	105 (100.0)	100 (100.0)	205 (100.0)
Completed Double-Blind Treatment Period	71 (67.6)	47 (47.0)	118 (57.6)
Discontinued in Double-Blind Treatment Period	34 (**32.4**)	53 (**53.0**)	87 (42.4)
Lack of Efficacy	12 (**11.4**)	35 (**35.0**)	47 (22.9)
Adverse Event	9 (8.6)	8 (8.0)	17 (8.3)
AE not due to opioid withdrawal	8 (7.6)	6 (6.0)	14 (6.8)
Opioid withdrawal-AE	1 (1.0)	2 (2.0)	3 (1.5)
Withdrew Consent	7 (6.7)	4 (4.0)	11 (5.4)
Protocol Violation	3 (2.9)	3 (3.0)	6 (2.9)
Investigator Opinion	3 (2.9)	1 (1.0)	4 (2.0)
Other	3 (2.9)	1 (1.0)	4 (2.0)
>3 days of <80% compliance with study medication	0	2 (2.0)	2 (1.0)
Lost to Follow-up	0	1 (1.0)	1 (0.5)
Sponsor Request	0	1 (1.0)	1 (0.5)
Modified Intent-to-Treat	**97 (92.4)**	**95 (95.0)**	**192 (93.7)**

From Applicant's Table 4, Study Report en3202031.pdf

The demographics and baseline characteristics were comparable for race, stabilized dose level and baseline pain ratings as noted in Table 10-2 in Dr. Fang's review. The oxymorphone ER group had more patients over age 65 (16%) compared to the placebo group (8%), more female patients (56% vs. 50%), and were heavier on average (195 lbs vs. 186 lbs). The heavier weight in the active group would, if anything, bias against efficacy for the active treatment. The larger number of older patients would potentially bias against safety for the active treatment.

As noted by Dr. Fang, the protocol deviations did not appear to be serious enough to impact efficacy results from these patients.

During titration, approximately 15% of patients received concomitant NSAIDs and 13% received an acetaminophen-containing product. During the double-blind period, 14% of patients received an acetaminophen-containing product. Seven percent were on antidepressants. Other products

used by up to 13% of patients included lipid lowering drugs, proton pump inhibitors, and stool softeners. Overall, concomitant medications were fairly well balanced across treatment groups.

Patients titrated to a wide range of oxymorphone doses. As shown in the table below, patients stabilized at total daily dose of 20 mg most commonly, followed by 40 mg, 30 mg, and 50 mg. Two patients did titrate to 140 mg of oxymorphone daily, even though opioid naïve previously. Based on the overall distribution and mean total daily dose of oxymorphone, the patients randomized to oxymorphone ER and placebo were fairly evenly distributed.

Table 4. Total Daily Dose of Oxymorphone at Which Patients Stabilized at Randomization, All Randomized Patients, Double-blind Period

	Oxymorphone ER	Placebo
Total Daily Dose mg	105	100
10	8	5
20	33	29
30	14	18
40	19	16
50	11	11
60	8	4
70	2	3
80	3	8
90	1	1
100	3	2
110	0	1
120	1	2
140	2	0
Mean (SD)	39.2 (26.4)	40.9 (25.3)

Source Applicant's Table, Appendix 16.2.2, Table 9, Study Report en3202031.pdf

Efficacy

The analysis of the primary efficacy endpoint, change in average VAS pain intensity over the prior 24 hours from baseline to final visit, showed a statistically significantly smaller change for the oxymorphone ER-treated patients than placebo-treated patients using the MITT population. Based on the design of this study, an ideal outcome would have been no change for the oxymorphone ER group and worsening for the placebo group. Based on the analysis, a worsening of pain over the 12-week double-blind period would be reflected as a positive score. As seen in the table below, both groups had positive scores but the change was smaller for the oxymorphone ER group than the placebo group. According to the Applicant, there was no substantial difference for the same analysis using the ITT population.

The Applicant's proposed method of imputing missing scores was appropriately conservative in that for patients who dropped out due to an adverse event, the worst case score was imputed. Therefore, if patients had an effect on pain intensity but could not tolerate study drug, a poor score was imputed.

Table 5. Mean Average Pain Intensity (VAS) and Mean Change from Baseline to Final Visit (Primary Analysis) – Modified Intent-to-Treat Population (Double-Blind Treatment Period)

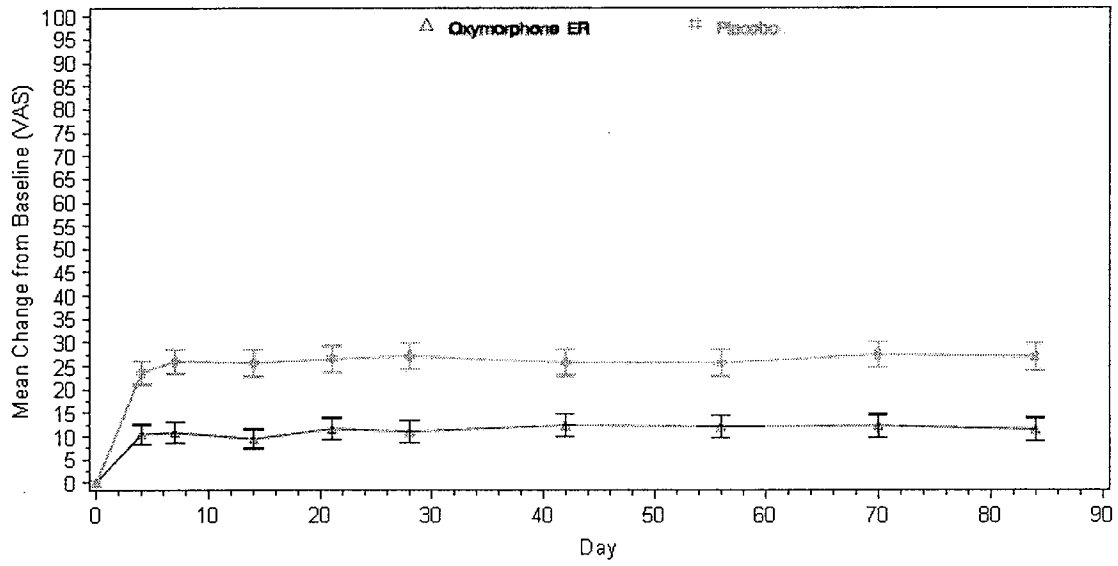
Statistics[a]	Oxymorphone ER (N=97)	Placebo (N=95)
Average Pain Intensity		
Baseline (Visit 5)		
Mean (STD)	**18.5** (11.22)	**19.3** (11.26)
Final Visit		
Mean (STD)	**29.9** (26.21)	**46.2** (27.03)
Change from Baseline to Final Visit		
Mean (STD)	11.4 (24.39)	26.9 (27.81)
LSMean ± SE	**10.6 ± 2.50**	**27.7 ± 2.53**
Treatment comparison vs. Placebo		
LSMean Difference	-17.1	--
95% CI	(-24.21, -10.04)	--
P-value	< 0.0001	--

Modified from Dr. Fang's Table 31-4

The secondary outcome measure, mean average pain intensity change by visit, illustrates the study results in the following figure. It is notable that the pain scores worsened from the end of titration and the start of the double-blind period through about Day 4, then became fairly stable through the end of the study. Day 4 is when rescue medication was restricted.

Figure 1. Mean Change in Baseline in Average Pain Intensity by Visit

Figure 3. Mean Change from Baseline in Average Pain Intensity (VAS) by Visit – Modified Intent-to-Treat Population (Double-Blind Treatment Period)



Data Source: Appendix 16.2.3, Figure 1.1
Average Pain Intensity VAS scores range from 0 mm=no pain to 100 mm=the worst pain imaginable.
Note: Error bars represent standard errors (+/-)

Source: Applicant's Figure 3, Study Report en3202031.pdf

Secondary endpoints, the change from baseline to final visit in patient's global assessment of pain medication and physician's global assessment of pain medication, an evaluation of compliance and study medication usage, and time to discontinuation due to lack of efficacy are summarized in the following table taken from Dr. Fang's review. The findings are all supportive of oxymorphone ER as more effective than placebo.

Table 6. Summary of Results for Secondary and Additional Efficacy Endpoints-MITT

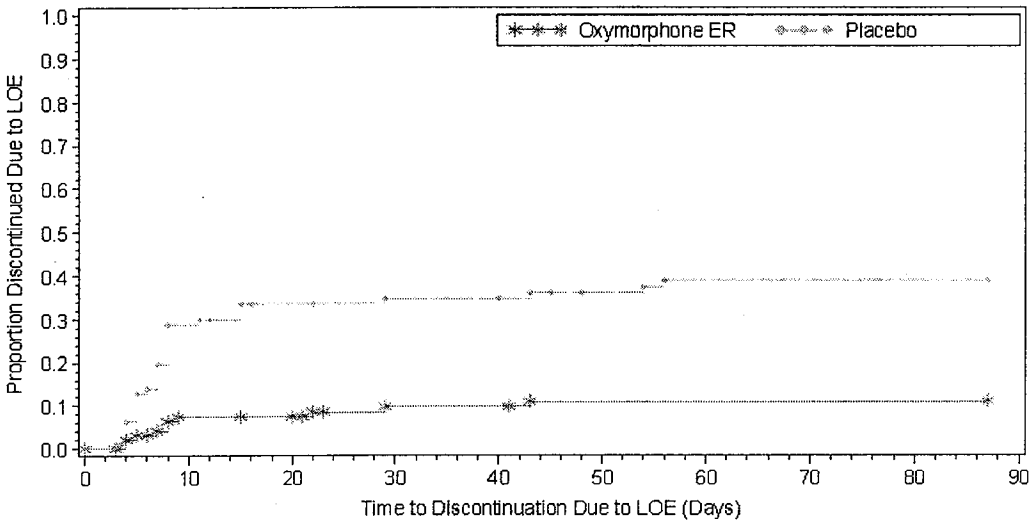
	Oxymorphone ER (N=97)	Placebo (N=95)	P value	Study report reference
Secondary endpoints				
Time to discontinuation due to lack of efficacy (see figure 2 below)			<0.0001	fig 2, p70
Number (%) discontinued due to lack of efficacy	10/97 (10.3%)	34/95 (35.8%)		table 14.1, p907
Patient global at final visit Proportion with good/very good/excellent	78/95 (82.2%)	34/86 (39.5%)	<0.0001	table 13, p72
Physician global at final visit Proportion with good/very good/excellent	80/96 (83.4%)	32/87 (36.7%)	<0.0001	table 14, p73
Additional endpoints				
Average PI by visit (see figure 1 above)				fig 3, p76
Change in PI with respect to stabilized dose level, LSMean	10.6	27.7	<0.0001	table 18.1, p913
Percent reduction in average PI (see figure 3 below)				fig 4, p81
Responders: ≥30% reduction in PI	79/97 (81.4%)	47/91 (51.7%)	<0.0001	fig 4, p81
Time to discontinuation due to all reasons (see figure 4 below)			<0.0007	fig 5, p82
Proportion discontinued due to all reasons	32/97 (33.0%)	52/95 (54.7%)		table 15.1, p908
Daily rescue in first four days of double-blind treatment	↑ from 2.2 mg to 3.3 mg	↑ from 2.3 mg to 10.3 mg		table 17, p85
% of days on rescue medication: Day 4 to final visit	34.4 - 41.2%	55.1 - 65.3%		table 33, p4117

From Dr. Fang's review, Table 10-8

The time to discontinuation due to lack of efficacy during the double-blind period shows a similar pattern as the average change in pain by visit. There is a flurry of dropouts until approximately Day 10. Rescue medication became limited on Day 4.

Figure 2. Time to Discontinuation Due to Lack of Efficacy

Figure 2. Time (Days) to Discontinuation Due to Lack of Efficacy During the Double-Blind Treatment Period—Modified Intent-to-Treat Population (Double-Blind Treatment Period)



Data Source: Appendix 16 2.2, Figure 2.1
p-value for treatment comparison between oxymorphone ER and placebo is <0.0001 and based on log-rank test.

Applicant's Figure 2, Study Report en3202031.pdf

Subgroup analyses were performed for the demographic and baseline characteristics. Younger patients randomized to oxymorphone ER had slightly greater worsening of pain than patients over 65 years for placebo but there was little difference in the oxymorphone group. Patients with severe baseline pain did have a greater worsening over the course of the double-blind period, as did patients who stabilized on a lower dose. Neither finding is surprising. Table 10-7 in Dr. Fang's review provides the details of these analyses.

Summary

Study 031, characterized by a titration to stabilized dose and randomization of responders to active treatment or placebo provides evidence of efficacy for oxymorphone ER in previously opioid naïve patients with chronic low back pain. The primary efficacy endpoint demonstrated a statistically significant difference in favor of active treatment with oxymorphone ER. The multiple secondary endpoints were supportive of this finding.

Study EN3202-032

Study EN3202-032 was to have been the same as Study EN3202-031 except that patients were to have been opioid tolerant defined as on a stable, fixed dose of around-the-clock opioid for LBP for at least 2 weeks prior to screening with reasonable tolerance of the opioid and expected to need a total daily oxymorphone ER dose in the range of 20-220mg (equivalent to oral morphine: 60-660mg). See Dr. Fang's review for the protocol review.

There were several post hoc analyses performed by the Applicant. The following bullets are taken from Dr. Fang's review.

- Mean change from baseline in average pain intensity (VAS) by visit using the imputation rules established for the primary analysis with an additional imputation rule that a previous post-baseline value was to be used to impute a missing "intermediate" post-baseline value.

- Time to discontinuation due to all reasons using the same method of analysis as for the endpoint of time to discontinuation due to lack of efficacy

- Percentage of responders defined as at least 30% percent reduction in average pain intensity (VAS) from screening to final visit, using a chi-square test of observed values (no data imputation)

- The percent reduction at all levels (≥10%, ≥20%, ≥30% ....) presented as a figure.

Results

A total of 251 patients entered open-label titration. One patient never received study drug. Of the remaining 250 patients, only 143 successfully completed the open-label titration period. The most common reason for discontinuation during the open-label titration was adverse events, accounting for 47 patients (19%). The next most common reason was failure to meet the titration-stabilization criteria for 17 patients (7%), consent was withdrawn by 15 patients, and 10 patients discontinued due to lack of efficacy. The reason for discontinuation was further investigated by Dr. Fang for those patients who discontinued due to withdrawn consent, Investigator Opinion, Other, and Sponsor Request. None of these patients' reason for withdrawal included either lack of efficacy or adverse events.

Table 7. Patient Disposition During Open-Label Titration Period: Number (%) of Patients

Patient Disposition	Oxymorphone ER
Entered Open-Label Titration Period	251 (100.0)
All Treated (Open-Label Titration Period)[a]	250 (99.6)
Not Treated[b]	1 (0.4)
Completed Open-Label Titration Period	143 (57.0)
Discontinued in Open-Label Titration Period	107 (42.6)
Adverse Event	47 (18.7)
AE not due to opioid withdrawal	47 (18.7)
Opioid withdrawal-AE	0
Patient did not meet Titration-Stabilization criteria	17 (6.8))
Withdrew Consent	15 (6.0)
Lack of Efficacy	10 (4.0)
Lost to Follow-up	6 (2.4)
Investigator Opinion	6 (2.4)
Protocol Violation	4 (1.6)
>3 days of <80% compliance with study medication	1 (0.4)
Other	3 (1.2)
Sponsor Request	2 (0.8)
Randomized and Entered Double-Blind Treatment Period	143 (57.0)

a All patients who received at least one dose of the Open-Label Titration medication.
b One patient was not treated according to Drug Accountability data.
Source: Applicant's Table 3 Study Report en3202032.pdf

During the double-blind period, there were further early discontinuations. The following table shows that only 49% of patients on oxymorphone ER completed the double-blind period compared to 18% of the patients randomized to placebo. The most common reason for dropout in the placebo patients was lack of efficacy, 53%, in contrast to 11% of patients in the oxymorphone ER group. Adverse events were responsible for 11% of placebo patient discontinuations including five patients (7%) who experienced opioid withdrawal. The protocol called for a best case score to be imputed for any patients who discontinue early due to opioid withdrawal, and as these were only in the placebo group, there would be no inadvertent bias in favor of active treatment due to these withdrawals. Adverse events were also responsible for an additional 10% of oxymorphone ER-treated patients discontinuing study participation early. The failure of four patients to sign the HIPAA consent form resulted in the exclusion of these four patients from the ITT population and all efficacy analyses were conducted on the remaining 138 patients, although all patients were included in the safety analysis. Further evaluation of the CRFs of patients who withdrew consent by Dr. Fang did not find these were due to adverse events.

Table 8. **Patient Disposition During the Double-Blind Treatment Period: Number (%) of Patients**

Table 4. Patient Disposition During the Double-Blind Treatment Period – Number (%) of Patients

Patient Disposition	Oxymorphone ER	Placebo	Overall
Randomized and Entered Double-Blind Treatment Period	70 (100.0)	73 (100.0)	143 (100.0)
All Treated Patients (Double-Blind Treatment Period)[a]	70 (100.0)	72 (98.6)	142 (99.3)
Not Treated[b]	0	1 (1.4)	1 (0.7)
Completed Double-Blind Treatment Period	49 (70.0)	18 (24.7)	67 (46.9)
Discontinued in Double-Blind Treatment Period[c]	21 (30.0)	54 (74.0)	75 (52.4)
Lack of Efficacy	8 (11.4)	39 (53.4)	47 (32.9)
Adverse Event	7 (10.0)	8 (11.0)	15 (10.5)
Opioid withdrawal-AE	0	5 (6.8)	5 (3.5)
AE not due to opioid withdrawal	7 (10.0)	3 (4.1)	10 (7.0)
Investigator Opinion	2 (2.9)	2 (2.7)	4 (2.8)
Withdrew Consent	1 (1.4)	2 (2.7)	3 (2.1)
Protocol Violation	2 (2.9)	1 (1.4)	3 (2.1)
Used prohibited medication for more than 3 consecutive days	0	1 (1.4)	1 (0.7)
Compliance with study medication is less than 80% for more than 3 days	1 (1.4)	0	1 (0.7)
Other	1 (1.4)	0	1 (0.7)
Lost to Follow-up	1 (1.4)	1 (1.4)	2 (1.4)
Sponsor Request	0	1 (1.4)	1 (0.7)
All Treated Patients (Double-Blind, Efficacy)[d]	69 (98.6)	69 (94.5)	138 (96.5)

Data Source: Appendix 16.2.2, Table 2
[a]All randomized patients who received at least one dose of the double-blind study medication.
[b]Patient 023-009 was randomized but not treated according to drug accountability data.
[c]Reasons for discontinuation are sorted in descending order of overall frequency.
[d]The following patients were excluded from the All Treated Patients (Double-Blind, Efficacy) population due to not signing the HIPAA consent form: 007-002 (Oxymorphone ER), 022-002 (Placebo), 022-004 (Placebo), 027-002 (Placebo).

From Applicant's Table 4, Study Report en3202032.pdf

The demographics and baseline characteristics were comparable for age, stabilized dose level and baseline pain ratings as noted in Table 10-11 in Dr. Fang's review. The oxymorphone ER group had more African American patients (15% vs. 7%, respectively), more female patients (57% vs. 33%, respectively) and were heavier on average (200 lbs vs. 191 lbs, respectively).

The heavier weight in the active group would, if anything, bias against efficacy for the active treatment.

In the Applicant's review of blinded data, a major protocol violation was identified in four patients who received randomized treatments without signing the HIPAA consent form. These patients were excluded from the efficacy analysis.

During titration, approximately 43% of patients received concomitant opioid analgesics, and 21% received a benzodiazepine. Thirteen percent received NSAIDs including selective COX-2 inhibitors and 10% received an acetaminophen-containing product. During the double-blind period, 21% of patients received a benzodiazepine, 14% of patients received an acetaminophen containing product. Twenty-three percent were on antidepressants, although these were more common in patients randomized to oxymorphone ER. Beta blockers were similar across the oxymorphone ER and placebo groups, 16% and 15%, respectively, but ACE inhibitors were 14% and 8%, I the oxymorphone ER and placebo groups, respectively. Other products used by up to 16% of patients included lipid lowering drugs, proton pump inhibitors, and stool softeners. As patients were on relatively stable doses of concomitant medications, it is unlikely that any of these differences were able to impact the efficacy results.

During titration, patients titrated to a wide range of oxymorphone doses. As shown in the table below, patients stabilized at total daily dose of 40 mg most commonly, followed by 60 mg, 20 mg, and 80 mg. Fourteen patients stabilized on doses of 200 mg or higher of oxymorphone daily, including one patient titrated to 260 mg of oxymorphone per day. Based on the overall distribution and mean total daily dose of oxymorphone, the patients randomized to oxymorphone ER and placebo were fairly evenly distributed.

Table 9. Stabilized Individual Dosing at Randomization of Double-Blind Treatment

	Oxymorphone ER (N = 70)	Placebo (N = 72)
Daily Dose (mg/day)	n (%)	n (%)
20	12 (17.1)	6 (8.3)
40	18 (25.7)	16 (22.2)
60	9 (12.9)	15 (20.8)
80	9 (12.9)	5 (6.9)
100	4 (5.7)	6 (8.3)
120	4 (5.7)	3 (4.2)
140	2 (2.9)	5 (6.9)
160	4 (5.7)	8 (11.1)
180	1 (1.4)	1 (1.4)
200	4 (5.7)	2 (2.8)
220	3 (4.3)	4 (5.6)
260	0	1 (1.4)
Mean (SD)	80.9 (59.3)	93.3 (61.2)

Source Applicant's Table 9, Appendix 16.2.2, Study Report en3202032.pdf

Efficacy

The analysis of the primary efficacy endpoint, change in average VAS pain intensity over the prior 24 hours from baseline to final visit, showed a statistically significantly smaller change for the oxymorphone ER-treated patients than placebo-treated patients using the ITT population. Based on the design of this study, an ideal outcome would have been no change for the

oxymorphone ER group and worsening for the placebo group. Based on the analysis, a worsening of pain over the 12-week double-blind period would be reflected as a positive score. As in Study 031, and as presented in the table below, both groups had positive scores but the change was smaller for the oxymorphone ER group than the placebo group.

The Applicant's proposed method of imputing missing scores was appropriately conservative in that for patients who dropped out due to an adverse event, a worst case score (screening) was imputed and for patients who dropped out due to opioid withdrawal, a best case score was imputed, baseline after titration. Therefore, if patients had an some benefit with pain intensity but could not tolerate study drug, a poor score was imputed. Similarly, a good score was imputed for those in the placebo group who dropped out due to opioid withdrawal, baseline after titration, again to avoid biasing in favor of study drug.

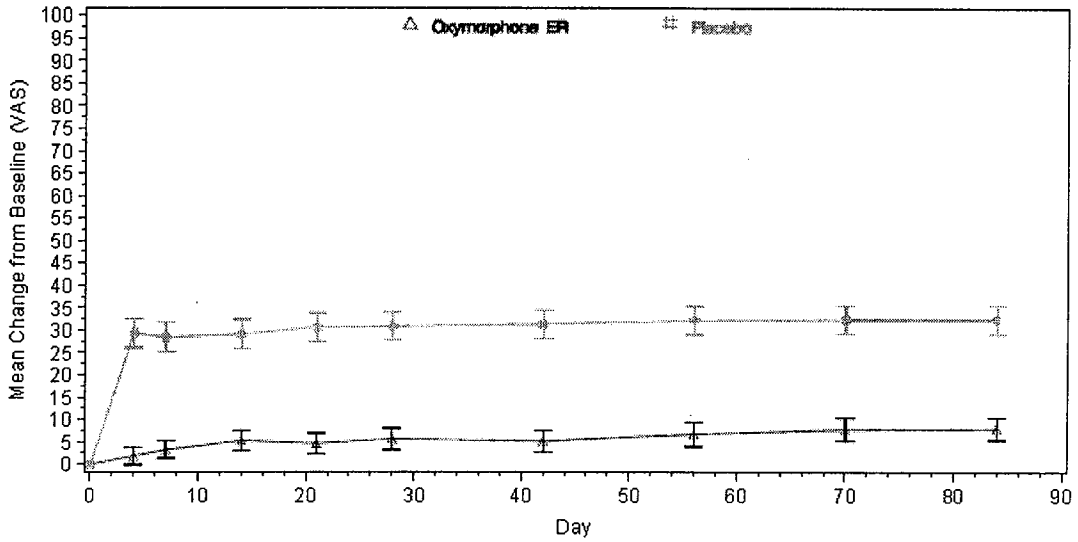
Table 10. Mean Average PI (VAS) and Mean Change from Baseline to Final Visit

Statistics[a]	Oxymorphone ER (N=69)	Placebo (N=69)
Average Pain Intensity		
Baseline (Visit 5)[b]	N=68	N=69
Mean (STD)	**23.9** (12.05)	**22.2** (10.75)
Final Visit	N=69	N=69
Mean (STD)	**31.3** (23.48)	**54.5** (28.43)
Change from Baseline to Final Visit	N=68	N=69
Mean (STD)	7.9 (20.60)	32.4 (27.00)
LSMean ± SE	**8.7 ± 2.95**	**31.6 ± 2.93**
Treatment comparison vs. Placebo		
LSMean Difference	-23.0	--
P-value	< 0.0001	--

[a]The Primary analysis used an ANCOVA model with treatment and center as effects, screening and baseline average pain intensity as covariates. The following imputation rules, for missing values, were used: Discontinued due to AE: Screening OCF; Discontinued due to Opioid withdrawal symptoms in placebo group: Baseline OCF; Discontinued for all other reasons: Last OCF;Patients who discontinued for all other reasons but without post-baseline pain score: Screening OCF. OCF= observation carried forward
[b]Oxymorphone ER patient 009-010 has a missing CRF/Visit Baseline value.
Source: Applicant's Table 12, Study Report en3202032.pdf

The mean average pain intensity change by visit is illustrated in the following figure. It is notable that the pain scores worsened from the end of titration through about Day 4, then became fairly stable through the end of the study. Day 4 is when rescue medication was restricted.

Figure 3. Mean Change from Baseline in Average Pain Intensity (VAS) by Visit – All Treated Patients (Double-Blind, Efficacy)



Data Source: Appendix 16.2.2, Figure 1
Note: Average pain intensity VAS scores range from 0 mm = no pain to 100 mm = the worst pain imaginable. Error bars represent standard errors (+/-).

Source: Applicant's Figure 3, Study Report en3202032.pdf

Secondary endpoints, the change from baseline to final visit in patient's global assessment of pain medication and physician's global assessment of pain medication, an evaluation of compliance and study medication usage, and time to discontinuation due to lack of efficacy are summarized in the following table taken from Dr. Fang's review. The post hoc analyses, proportion of responders, proportion discontinued due to all reasons The findings are all supportive of oxymorphone ER as more effective than placebo.

Appears This Way
On Original

Table 11. Summary of Results for Secondary and Additional Efficacy Endpoints-MITT

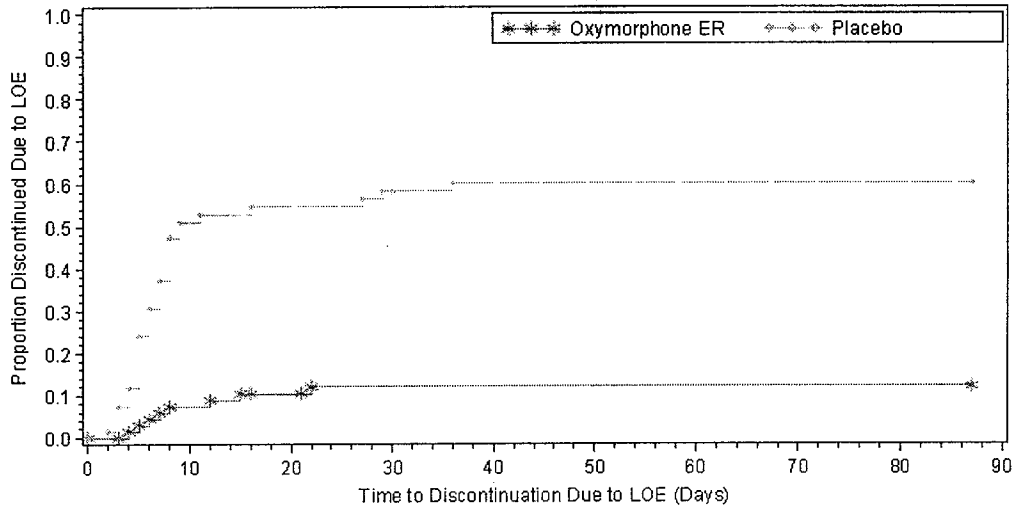
	Oxymorphone ER (N=69)	Placebo (N=69)	P value	Study report reference
Secondary endpoints				
Time to discontinuation due to lack of efficacy (see figure 5 below)			<0.0001	fig 2, p71
Number (%) discontinued due to lack of efficacy	8/69, (11.6%)	37/69, (53.6%)		table 14, p656
Patient global at final visit Proportion with good/very good/excellent	55/69 (79.7%)	22/67 (32.8%)	<0.0001	table 13, p73
Physician global at final visit Proportion with good/very good/excellent	58/69 (84.5%)	18/65 (27.7%)	<0.0001	table 14, p74
Change in PQAS-20 baseline to final visit LSMean	5.5	40.5	<0.0001	table 18, p667
Additional endpoints				
Average PI by visit (See figure 6 above)				fig 3, p76
Change in PI with respect to stabilized dose level, LSMean	8.6	31.6	<0.0001	table 19, p668
Percent reduction in average PI (see figure 7 below)				fig 4, p81
Responders: ≥30% reduction in PI	55/69 (79.7%)	23/66 (34.8%)	<0.0001	
Time to discontinuation due to all reasons (see figure 8 below)			<0.0001	fig 5, p82
Proportion discontinued due to all reasons	20/69 (29.0%)	51/69 (73.9%)		table 15, p657
Daily rescue in first four days of double-blind treatment	↑ from 5.6 mg to 6.5 mg	↑ from 11.0 mg to 15.6 mg		table 17, p85
% of days on rescue medication: Day 4 to final visit	61.8-70.7%	62.2-66.7%		table 34, p697

From Dr. Fang's review, Table 10-8

The time to discontinuation due to lack of efficacy during the double-blind period shows a similar pattern to the average change in pain by visit. Again, there is a marked flurry of dropouts between Days 4 and 8, but there are ongoing dropouts due to lack of efficacy through Day 22 for the oxymorphone ER patients and Day 36 for placebo patients. Rescue medication became limited on Day 4.

Figure 4. Time to Discontinuation Due to Lack of Efficacy

Figure 2. Time (Days) to Discontinuation Due to Lack of Efficacy During the Double-Blind Treatment Period – All Treated Patients (Double-Blind, Efficacy)



Data Source: Appendix 16.2.2, Figure 2
Note: p-value for treatment comparison between oxymorphone ER and placebo is <0.0001 and based on log-rank test.

Applicant's Figure 2, Study Report en3202032.pdf

Subgroup analyses were performed for the demographic and baseline characteristics. Younger patients randomized to oxymorphone ER had slightly greater worsening of pain that patients over 65 years, but the converse is true for placebo. This is the reverse of what was found in Study 031. Patients with severe baseline pain did have a greater worsening over the course of the double-blind period, as did patients who stabilized on a lower dose. Neither finding is surprising. Table 10-16 in Dr. Fang's review provides the details of these analyses.

Summary

Study 032, characterized by a titration to stabilized dose, followed by randomization of responders to active treatment or placebo provides evidence of efficacy for oxymorphone ER in previously opioid-tolerant patients with chronic low back pain. The primary efficacy endpoint demonstrated a statistically significant difference in favor of active treatment with oxymorphone ER. The multiple secondary endpoints were supportive of this finding.

Overall Summary of Efficacy of Oxymorphone ER

Studies 031 and 032 demonstrate evidence of efficacy of oxymorphone ER in managing chronic pain in patients who were opioid naïve and opioid tolerant, respectively.

The question arises of how worsening pain scores on active treatment can support a finding of efficacy. One explanation is the development of opioid tolerance, particularly in a formerly opioid naïve population, This does not appear likely as most of the change occurred during the first week and then pain scores were fairly constant over remaining 11 weeks of the double-blind period. Tolerance would more likely have appeared as a more gradual change over time. Another explanation is that the protocol imposed limitation on rescue medication contributed to

worsened pain. Chronic pain is known to fluctuate and a modified-release product with limited rescue may not be sufficient to manage the fluctuations. This hypothesis is supported by the time to discontinuation which shows a marked flurry of dropouts between Days 4 and 8. Rescue medication became limited on Day 4. As this finding likely reflects constraints imposed by study participation and there is a consistently better response by patients in the active treatment group, this study can be considered support for a finding of efficacy.

As with Study 031, in Study 032, the change in pain intensity lessened for both groups, more so for the placebo group. The pattern of change with respect to pain scores as well as time to discontinuation due to lack of efficacy similarly supports the likelihood that the primary reason for the worsening of pain scores early on was limitation of rescue. In this opioid-experienced population, it seems even less likely that this was due to tolerance. The time to discontinuation and the number of days during which pain intensity worsened both reflect a change early in the double-blind period. Similarly, there is a consistently better response by patients in the active treatment group, and this study can also be considered support for a finding of efficacy.

As an enrichment design in which only those who could be successfully titrated were randomized, one can argue that the results may not be generalizable to the wider chronic pain population. However, it is characteristic of chronic analgesic trials of opioids to have a large percentage of patients dropout due to adverse events and for efficacy to be demonstrated in only a percentage of patients enrolled. When the patients who dropout due to adverse events are among the randomized population, there is a large amount of missing data and therefore a need to impute data for the primary efficacy analysis. Imputation generally creates bias, and depending on the method chosen, can bias in favor or against the study drug. By enriching the randomized population for patients who can potentially be successfully treated with study drug, the problem of dropouts can be reduced, thereby reducing the amount of data that must be imputed. This allows the efficacy to be more clearly demonstrated. To permit an understanding of the generalizability of the results, the number of patients who fail to successfully titrate must be kept in consideration when reporting the study outcomes.

OXYMORPHONE IR

Overview of Original Application – Oxymorphone IR

Study EN3203-004 was a 48-hour, single and multi-dose, placebo- and active-controlled study in 300 patients with post-operative pain due to knee or hip total or partial arthroplasty involving osteotomy. The results of the primary efficacy endpoint, TOTPAR 0-8, along with secondary analyses of pain relief and change in pain intensity following the single dose period demonstrate that the oxymorphone IR 10, 20, and 30 mg doses were effective when compared with placebo. Effects of exclusion of patients based on the Sponsor's definition of the evaluable population were explored in additional analyses which yielded the same results. An immediate-release formulation of oxycodone was not effective when compared with placebo. Additional analyses continued to support findings of efficacy, but not consistently for the oxymorphone IR 10, 20, and 30 mg doses. The proportion of patients experiencing 50% pain relief and the median time to 50% pain relief were statistically significantly greater for the oxymorphone IR 10 and 20 mg groups compared to placebo. Time to first perceptible pain relief did not differ between the active treatment groups and placebo while time to meaningful pain relief was statistically

significantly shorter for the three oxymorphone IR groups compared to placebo. The median time to re-medication was statistically significantly longer for the oxymorphone IR 20 and 30 mg groups compared to placebo. Review of mean PR and PID scores at individual study time points failed to demonstrate any superiority of the oxymorphone IR 30 mg group over the oxymorphone IR 20 mg group while the data trended in favor of the oxymorphone IR 20 mg dose. The patient global evaluation of satisfaction with study medication was statistically significantly better for the oxymorphone IR 10 and 20 mg groups compared to placebo, but not for the oxymorphone IR 30 mg group.

The nature of the study design during the multi-dose period precluded drawing conclusions about efficacy during this portion of the study. During this time period, patients requiring remedication prior to three hours after the last dose or rescue medication were withdrawn from the study. The Sponsor attempted to determine the dosing interval of oxymorphone IR during this study period. The analysis of the dosing interval performed by the Sponsor suggests a dosing interval of 7 to 9 hours. However, this analysis fails to account for subjects being withdrawn from the study for requiring rescue medication within 3 hours of study medication dosing, and for subjects receiving rescue medication after 3 hours of study medication dosing. Further support that the dosing interval for oxymorphone IR is not 7 to 9 hours comes from the finding that more than half of the study patients on oxymorphone IR 10 mg withdrew from the study by Hour 4 and for patients on oxymorphone IR 20 mg and 30 mg, by Hour 5.

Study EN3203-005 was a single-dose, double-blind, placebo-and active-control study of oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone 15 mg, and oxycodone 30 in 324 patients with postoperative pain due to orthopedic procedures involving osteotomy. The results support a finding of efficacy for oxymorphone IR 20 mg as well as the two oxycodone IR doses using the primary efficacy endpoint, TOTPAR 0-8, as well as nearly all of the secondary outcome measures. There was no efficacy demonstrated for the oxymorphone IR 10 mg dose. Effects of an evaluable population excluding subjects requiring rescue medication within the first hour were explored in alternate analyses of the primary outcome utilizing a more inclusive population. No differences in the outcomes were found. Patient global assessment of pain relief mirrored these findings. For patients in the oxymorphone IR 20 mg group not requiring rescue medication in the first hour, the median time to rescue was nearly 5 hours.

NEW EFFICACY STUDIES – Oxymorphone IR
The current submission consists of new data from two completed adequate and well controlled efficacy studies,.

Study EN3203-009
Protocol
Study EN3203-009 was a randomized, double-blind, placebo- and active-controlled, parallel, single- and multiple-dose (48 hours), study of oxymorphone IR in patients with moderate to severe pain following abdominal surgery.

Enrollment was to be patients scheduled for surgery through an abdominal incision of at least 3 cm, anticipated hospitalization for at least 36 hours, need of oral opioid therapy for at least 48 hours, anticipated treatment with short-acting parenteral analgesia post-operatively. Patients

were to be capable of undergoing a washout within 12 hours of the last dose of parenteral opioids (washout ≥45 minutes from IV analgesics and ≥4 hours from IM analgesics) and anticipated conversion to oral analgesics within 30 hours following surgery.

Initial post-operative analgesia was to have been an opioid by IV PCA or non-PCA or IM, but not by epidural route. Following a washout from parenteral analgesia, patients with moderate to severe pain on a categorical scale and pain rated ≥50 mm on a 100-mm visual analog scale (VAS) were to be randomized to one of the four treatment groups to take study drug every four to six hours. Study treatment groups were oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone IR 15 mg and placebo. After the initial 6-hour period, dosing was to be every four to six hours.

Patients able to complete the first six-hour period and requiring rescue within four to six hours were to enter the multiple-dose period. Those requesting re-medication within the first four hours were to be discontinued from the study.

During the 48-hour multiple-dose period which was to follow the initial dose, patients were to complete a diary/electronic diary for dosing and pain assessments prior to each dose of the study medication. Those in need of re-medication sooner than every four hours between doses were to be discontinued from the study.

The primary efficacy endpoint was to be the time to discontinuation due to all causes during the entire study. Secondary efficacy endpoints for the multiple-dose period were planned to include mean average pain intensity (PI) (the average pain during each dosing interval evaluated at the time prior to each additional dose) and mean current PI (which represented the end-of-dosing pain evaluated also at the time prior to each additional dose), and patient global and physician global evaluation of study medication (recorded at the end of 48 hours). Secondary efficacy endpoints for the single-dose period were to include sum of pain intensity differences (SPID), total pain relief (TOTPAR), hourly pain relief (PR) and hourly pain intensity difference (to be recorded at 15, 30, 45, and 60 minutes, 1.5 hours, 2 hours, and hourly thereafter through Hour 6 using both categorical and VAS scales), and time to the first perceptible and meaningful pain relief (by double stopwatch) for the single-dose period.

Safety and tolerability were planned to be evaluated by monitoring adverse events (AEs) throughout the study.

The analysis population was to be the ITT population defined as all randomized patients who received at least one dose of double-blind study medication and completed one post-dose efficacy assessment. Imputation of missing scores for the secondary analyses was to be based on the reason the data was missing. For patients who discontinued early or took the second dose of study medication prior to the 6-hour mark, baseline observation carried forward (BOCF) was to be used. For missing individual assessments, data was to be interpolated linearly. For PR, a score of zero was used in the BOCF method for discontinuation due to an AE. For patients who took a second dose, the last observation carried forward (LOCF) method was applied to PR and PI. For patients who took a second dose prior to completion of the initial six hours of assessments, the LOCF method was used to carry the last pain score collected in the Single-Dose Period to Hour 6.

Post hoc changes to the analysis plan are described in Dr. Fang's review.

Results

A total of 331 patients were enrolled and received at least one dose of study medication. One patient who received one dose of study drug was consented after surgery and so was excluded from all efficacy analyses. Two patients were excluded from the secondary efficacy analyses due to no post-dose data. Usually these patients would be included in the ITT population, but as they were included in the primary efficacy analysis, and there were only two patients, there is no need to reanalyze the secondary endpoints.

Disposition is displayed in the following table. During the single-dose and multiple-dose periods, the placebo patients had the highest rate of discontinuation due to lack of efficacy. Discontinuations due to adverse events were highest for the oxymorphone IR 20 mg-group in the single-dose period, and for the oxymorphone 10 mg group during the multiple-dose period.

Table 12. Disposition

Patient Disposition n (%)	Oxymorphone IR 10 mg (N=82)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)	Total (N=331)
Randomized	82	81	83	85	331
All Treated Patients	82 (100.00)	81 (100.00)	83 (100.00)	85 (100.00)	331 (100.00)
Multiple-Dose Period (0-48 Hours)					
Completed treatment Period	31 (37.80)	32 (39.51)	34 (40.96)	15 (**17.65**)	112 (33.84)
Discontinued	**51 (62.20)**	**49 (60.49)**	**49 (59.04)**	**70 (82.35)**	219 (66.16)
Lack of Efficacy	34 (41.46)	25 (**30.86**)	33 (39.76)	53 (**62.35**)	145 (43.81)
Adverse Event	7 (**8.54**)	14 (**17.28**)	11 (13.25)	11 (12.94)	43 (12.99)
Withdrew Consent	9 (10.98)	7 (8.64)	4 (4.82)	5 (5.88)	25 (7.55)
Protocol Violation	1 (1.22)	1 (1.23)	0 (0.00)	1 (1.18)	3 (0.91)
Withdrew by Investigator	0 (0.00)	1 (1.23)	0 (0.00)	0 (0.00)	1 (0.30)
Other	0 (0.00)	1 (1.23)	1 (1.20)	0 (0.00)	2 (0.60)
Intent-to-Treat Patients	81 (98.78)	81 (100.00)	83 (100.00)	85 (100.00)	330 (99.70)
Single-Dose Period (0-6 Hours)					
Completed treatment Period	48 (58.54)	53 (65.43)	49 (59.04)	45 (52.94)	195 (58.91)
Discontinued	**34 (41.46)**	**28 (34.57)**	**34 (40.96)**	**40 (47.06)**	136 (41.09)
Lack of Efficacy	29 (35.37)	21 (**25.93**)	27 (32.53)	35 (**41.18**)	112 (33.84)
Adverse Event	5 (6.10)	4 (4.94)	4 (4.82)	4 (4.71)	17 (5.14)
Withdrew Consent	0 (0.00)	1 (1.23)	3 (3.61)	1 (1.18)	5 (1.51)
Withdrew by Investigator	0 (0.00)	1 (1.23)	0 (0.00)	0 (0.00)	1 (0.30)
Other	0 (0.00)	1 (1.23)	0 (0.00)	0 (0.00)	1 (0.30)
Intent-to-Treat Patients	80 (97.56)	80 (98.77)	83 (100.00)	85 (100.00)	330 (99.70)

Source: Applicant's Table 2, en3203009.pdf

Baseline and demographic characteristics were well balanced across treatment groups. More than 98% of the patient population was female in this study. The mean age was 42 to 43 years across the treatment groups. Baseline pain was comparable by VAS score across treatment groups averaging 62 to 65 mm. Using the categorical scale, there were fewer severe ratings in the oxymorphone IR 20 mg group. See Dr. Fang's review for further details.

Concomitant medications were primarily stool softeners and laxatives, antibiotics, serotonin 5HT3 antagonists, and estrogens. There were differences in the frequency of use of these products across the treatment groups as demonstrated in the following table. It is unlikely that any of the imbalances noted would alter efficacy outcomes.

Table 13. Concomitant Medications

Table 5. Summary of Concomitant Medications Taken by at Least 5% of Patients – All Treated Patients

ATC Class	Oxymorphone IR 10 mg (N=82) n (%)	Oxymorphone IR 20 mg (N=81) n (%)	Oxycodone IR 15 mg (N=83) n (%)	Placebo (N=85) n (%)
Number of Patients with at Least One Concomitant Medication	67 (81.71)	68 (83.95)	63 (75.90)	69 (81.18)
Softeners, Emollients	13 (15.85)	14 (17.28)	11 (13.25)	12 (14.12)
Contact Laxatives	9 (10.98)	16 (19.75)	10 (12.05)	10 (11.76)
Cephalosporins and Related Substances	15 (18.29)	8 (9.88)	14 (16.87)	6 (7.06)
Serotonin 5HT3 Antagonists	10 (12.20)	14 (17.28)	9 (10.84)	8 (9.41)
Aminoalkyl Ethers	11 (13.41)	12 (14.81)	13 (15.66)	4 (4.71)
Anilides	6 (7.32)	10 (12.35)	11 (13.25)	3 (3.53)
Natural and Semisynthetic Estrogens, Plain	5 (6.10)	8 (9.88)	8 (9.64)	7 (8.24)
Multivitamins, Other Combinations	9 (10.98)	5 (6.17)	4 (4.82)	7 (8.24)
Other Drugs for Functional Bowel Disorders	8 (9.76)	7 (8.64)	5 (6.02)	5 (5.88)
Selective Serotonin Reuptake Inhibitors	6 (7.32)	5 (6.17)	8 (9.64)	4 (4.71)
Thyroid Hormones	7 (8.54)	3 (3.70)	7 (8.43)	6 (7.06)
H2-Receptor Antagonists	4 (4.88)	5 (6.17)	4 (4.82)	4 (4.71)

Source: Applicant's Table 5, EN3203009.pdf

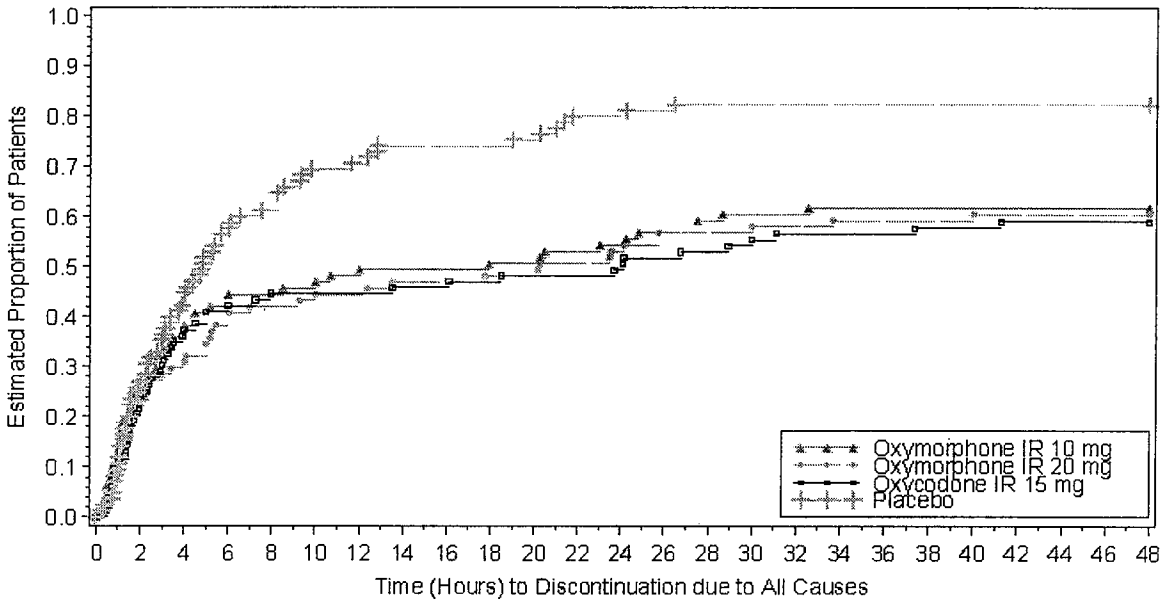
Efficacy

The primary efficacy endpoint was time to discontinuation due to all causes during the 48-hour treatment period. There were statistically significant differences favoring all three active treatment groups compared to placebo. The median time to discontinuation was 17 hours and 55 minutes for the oxymorphone IR group, 20 hours and 15 minutes for the oxymorphone IR 20 mg group, 24 hours and 5 minutes for the oxycodone IR 15 mg group and four hours and 50 minutes for the placebo group.

The Kaplan-Meier curves for this analysis clearly illustrate the differences between the active treatment groups and placebo.

Figure 5. Time to Discontinuation

Figure 2. Time (Hours) to Discontinuation Due to All Causes – Intent-to-Treat Patients – Multiple-Dose Period (0-48 Hours)



Source: Applicant's Figure 2, EN3203009.pdf

It is notable that while there were fewer dropouts in the active treatment groups, there was a substantial proportion of patients who discontinued early from all three active treatment groups. While patients undergoing surgery are frequently treated with oral opioid analgesics in the postoperative period, it is usually in the context of individualization of the dose, both amount and frequency of dosing. The lack of flexibility in dosing in the context of a clinical trial of an opioid analgesic likely contributes substantially to early discontinuations and cannot be taken as evidence of lack of efficacy or tolerability. The presence of the oxycodone IR treatment group provides an opportunity to compare the oxymorphone IR doses to an approved product recognized as safe and effective. The behavior of patients in the oxycodone IR treatment group is very similar to the oxymorphone IR treatment groups.

The secondary efficacy endpoints are described in detail in Dr. Fang's review. Mean average PI over the 48-hour treatment period was statistically significantly lower for the active treatment groups compared to placebo. The mean PI just prior to the next dose was also statistically significantly lower for the active treatment groups as compared to placebo. The patient global evaluation of study medication was statistically significantly better for the two oxymorphone IR groups compared to placebo. The oxycodone group trended better than placebo. The time specific analysis of PI difference and PR during the first 6-hour dosing interval showed the longest periods of statistically significant improvement compared to placebo for the oxymorphone IR 20 mg group. See Dr. Fang's review for the details of these analyses.

Multiple analyses of single-dose effects were performed and supported the efficacy of the active treatment groups although not all comparisons with placebo met statistical significance. There were generally greater differences for the oxymorphone IR 20 mg group as compared to the oxymorphone 10 mg group.

The median time to onset was 40 minutes for the oxymorphone IR 10 mg group, 34 minutes for the oxymorphone IR 20 mg group and 45 minutes for the oxycodone IR 15 mg group.

The median time to remedication during the first 6-hour dosing interval was four hours for all treatment groups. While there were no statistically significant differences from placebo, this is a descriptive measure used to inform dosing interval and supports the currently proposed dosing interval of every four to six hours.

Summary
Study 009 was a double-blind, placebo-controlled and active-controlled study of oxymorphone IR 10 mg and 20 mg every four to six hours in the postoperative setting. This study primarily enrolled women. There is evidence for efficacy of the two doses of oxymorphone studied compared to placebo, and overall similar results to the oxycodone IR 15 mg treatment group. There was evidence of a dose response across the two oxymorphone doses.

Study 3203-008
Study 3203-008 was a randomized double-blind, eight-hour study of the analgesic efficacy and safety of oxymorphone IR 5 mg in patients following ambulatory arthroscopic knee surgery. Oxymorphone IR 5 mg was compared to placebo in patients once their postoperative pain reached mild to moderate on a categorical scale or between 30-70mm on a VAS. Patients could dose as frequently as every hour for an eight-hour period.

One hundred twenty two patients were enrolled. Mean pain intensity difference over the eight-hour treatment period did reveal a statistically significant difference between treatment groups, but 93% of the oxymorphone IR 5 mg patients redosed at one hour, 78% redosed at 2 hours, and 65% redosed at 3 hours. In comparison, 81% of placebo patients redosed at one hour, 63% at 2 hours and 45% at 3 hours. The mean dose interval was 1.9 hours for the oxymorphone IR group and 1.6 hours for placebo. While there is evidence of analgesic efficacy for oxymorphone IR from this study, the results do not support 5 mg as an effective dose.

Overall Summary of Efficacy of Oxymorphone IR

Studies 004 and 009 provide evidence of efficacy for oxymorphone IR 10 and oxymorphone IR 120 in two postoperative pain populations. Study 004 explored patients undergoing knee or hip total or partial arthroplasty involving osteotomy. Study 009 studied patients undergoing non-laparoscopic abdominal surgery. The mean age of patients in Study 004 was approximately 62 years and included patients over 90 years of age. In Study 009 the mean age was approximately 42 years of age. Efficacy during the multiple-dose period of this Study 004 was difficult to fully interpret due to the availability of additional analgesic medication greater than three hours after dosing of study medication at the discretion of the Investigator. The lack of available rescue in

Study 009 provided results during the multiple-dose period that did not have this limitation and provide support for the finding of multiple-dose efficacy.

In Study 004, there was no benefit evident for the oxymorphone IR 30 mg dose over the 20 mg dose, but as will be discussed in the evaluation of safety, there were a clinically meaningful increase in serious adverse events, particularly hypoxia for the 30 mg dose, indicating that it is not an appropriate initial dose of oxymorphone in the immediate postoperative period.

The currently proposed dosing interval of every four to six hours is supported by the median time to remedication of four hours in Study 009 and the prior finding that more than half of the study patients on oxymorphone IR 10 mg withdrew from the study by Hour 4 and for patients on oxymorphone IR 20 mg and 30 mg, by Hour 5.

Study EN3203-005 was a single-dose, double-blind, placebo-and active-control study of oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone 15 mg, and oxycodone 30 in 324 patients with postoperative pain due to orthopedic procedures involving osteotomy. The results support a finding of efficacy for oxymorphone IR 20 mg as well as the two oxycodone IR doses using the primary efficacy endpoint, TOTPAR 0-8, as well as nearly all of the secondary outcome measures. There was no efficacy demonstrated for the oxymorphone IR 10 mg dose. Effects of an evaluable population excluding subjects requiring rescue medication within the first hour were explored in alternate analyses of the primary outcome utilizing a more inclusive population. No differences in the outcomes were found. The patient global assessment of pain relief mirrored these findings. For patients in the oxymorphone IR 20 mg group not requiring rescue medication in the first hour, the median time to rescue was nearly 5 hours.

INTEGRATED ANALYSIS OF SAFETY

Extent of Exposure

In the original application, there were 2542 unique patients in the oxymorphone clinical development program, 2108 of these patients in the Phase 2/3 program, and 1484 unique patients in oxymorphone ER Phase 2/3 clinical trials, 1089 of whom received oxymorphone ER and/or IR at some point. The remainder received oxycodone ER or IR, morphine ER, or placebo. There were 624 unique patients in oxymorphone IR Phase 2/3 clinical trials.

Extent of Exposure- Oxymorphone ER

In the current submission, a total of 2575 unique patients were enrolled in oxymorphone ER Phase 2/3 clinical trials, including 2011 who received oxymorphone ER. A total of 1828 subjects received oxymorphone ER as their last treatment in Phase 2/3 studies; 807 of these patients are from open-label Phase 2/3 studies. The following table describes the exposure to oxymorphone ER by dose and duration in placebo- and active-controlled clinical trials.

Table 14 Extent of Exposure by Treatment Duration and Modal Daily Dose–Phase 2/3 ER Trials

	Oxymorphone ER dosage (mg/day) [a]				
	≤10	>10-50	>50-90	>90	Total
Duration [b]	Number (%) of subjects on treatment				
1 - 3 Days	65 (18.8)	238 (69)	19 (5.5)	23 (6.7)	345 (100)
4 - 10 Days	67 (10.9)	332 (54.2)	118 (19.3)	95 (15.5)	612 (100)
11 - 17 Days	14 (5.8)	195 (81.3)	20 (8.3)	11 (4.6)	240 (100)
18 - 24 Days	2 (3.3)	40 (65.6)	11 (18)	8 (13.1)	61 (100)
25 - 31 Days	2 (6.9)	16 (55.2)	7 (24.1)	4 (13.8)	29 (100)
3 Months	13 (3.8)	173 (50.3)	72 (20.9)	86 (25)	344 (100)
6 Months	16 (10.1)	54 (34)	29 (18.2)	60 (37.7)	159 (100)
9 Months	0 (0.0)	15 (24.2)	21 (33.9)	26 (41.9)	62 (100)
12 Months	0 (0.0)	45 (45)	25 (25)	30 (30)	100 (100)
> 12 Months	0 (0.0)	21 (51.2)	14 (34.1)	6 (14.6)	41 (100)
> 18 Months	0 (0.0)	7 (58.3)	4 (33.3)	1 (8.3)	12 (100)
Total	179 (9)	1129 (56.6)	336 (16.9)	349 (17.5)	1993 (100)
Patient Years [c]	12.21	163.42	92.35	102.88	370.87

[a] No dosing information is available for 18 patients and they are therefore excluded from this table.
[b] Total duration of exposure for all trials in which a patient participated.
[c] Patient years: the total number of days in a given modal dose group divided by 365.25.
Note: The information in the table represented the exposure to oxymorphone over time based on the most frequent dose the patient took, not each patient's total exposure.
Based on Studies EN3202-012, 015, 016, 017, 018, 019, 025, 028, 029, 031, and 032.
Source: Applicant Table 7, safety.pdf.

The following table presents the cumulative open-label exposure by study and duration on treatment. The overall exposure includes 433 patients with at least six months exposure and 267 patients with exposure of one year duration or longer.

Table 15 Extent of Cumulative Exposure in Open-Label Phase 2/3 Oxymorphone ER Trials

	Months on treatment [a]					
	3 Months	6 Months	9 Months	12 Months	18 Months	≥24 Months
Study (duration)	Number (%) of subjects on treatment					
020 (2-year)	197 (100)	104 (52.8)	94 (47.7)	86 (43.7)	42 (21.3)	26 (13.2)
021 (1-year)	239 (100)	160 (66.9)	126 (52.7)	111 (46.4)	3 (1.3)	0 (0.0)
022 (1-year)	24 (100)	9 (37.5)	7 (29.2)	7 (29.2)	7 (29.2)	1 (4.2)
028 (6-month)	124 (100)	63 (50.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
029 (1-year)	220 (100)	97 (44.1)	74 (33.6)	63 (28.6)	0 (0.0)	0 (0.0)
Total	804 (100)	433 (53.9)	301 (37.4)	267 (33.2)	52 (6.5)	27 (3.4)

[a] No dosing information was available for three patients (two in Study 028, one in Study 029) and therefore, they were excluded from this table.
Note: total exposure to oxymorphone was calculated on a per patient basis regardless of dose or changing doses for a patient within a study.
Source: Applicant Table 6, safety.pdf.

Extent of Exposure- Oxymorphone IR

In total, 788 unique subjects received at least one dose of oxymorphone IR in clinical trials of oxymorphone IR, including 34 cancer patients who received oxymorphone IR during active-controlled trials (EN3202-018 and EN3202-019). A total of 554 patients received oxymorphone IR in Phase 2/3 IR trials. Table from Dr. Fang's review provides a breakdown of patient numbers by study and treatment assignment.

Table 16. Summary of Exposure by Subset and Treatment Groups in All Oxymorphone IR Trials

Treatment	Oxymorphone IR			Oxycodone IR			Placebo		
Database	ISS	Update	Overall	ISS	Update	Overall	ISS	Update	Overall
All Trials	565	223	**788**	195	83	278	122	147	269
Phase 1	197	0	197	0	0	0	0	0	0
Phase 2/3	368	223	591	195	83	278	123	147	270
Phase 2/3 IR post-op pain	334	223	**557** [a]	195	83	278	123	147	270
EN3203-004 [a]	204			67			57		
EN3203-005	130			128			66		
EN3202-008		60			0			62	
EN3202-009		163			83			85	
Phase 2/3 ER cancer pain	34	0	34	0	0	0	0	0	0
EN3202-018	18								
EN3202-019	16								

[a] In Study 3203-004, 21 placebo patients were re-randomized to one of the three oxymorphone IR treatment groups (oxymorphone IR 10 mg: six patients; oxymorphone IR 20 mg: eight patients; oxymorphone IR 30 mg: seven patients); seven placebo patients were re-randomized to oxycodone IR. These 21 patients are presented in the table under both the active (oxymorphone or oxycodone) and the placebo treatment groups.
Source: Dr. Fang's Table 7- **10** (Table 50 on page 52 of the ISS, Table 2 on page 42 of the report for Study 3203-009, and page 68 of the report for Study 3203-008.)

The following table taken from Dr. Fang's review breaks down the exposure to oxymorphone IR by number of doses and duration of exposure.

Table 17. Exposure To Oxymorphone IR By Number Of Doses And Duration Of Exposure.

Dose		Single dose	>1 dose	# of dose/ patients		Duration (hours)	
				Mean	Maximum	Mean	Maximum
5 mg	Study 3203-008	N=60	N=56	5 doses	8 doses	7 hours	36 hours
10 mg	Study 3203-005	N=63					
	Study 3203-004	N=65	N=34	3 doses	11 doses	17 hours	51 hours
	Study 3203-009	N=82	N=48	5 doses	16 doses	21 hours	80 hours
	Subtotal	***N=270***	***N=82***				
20 mg	Study 3203-005	N=67					
	Study 3203-004	N=67	N=47	4 doses	13 doses	21 hours	57 hours
	Study 3203-009	N=81	N=53	5 doses	13 doses	23 hours	59 hours
	Subtotal	***N=215***	***N=100***				
30 mg	Study 3203-004	N=72	N=37	3 doses	9 doses	16 hours	63 hours
	Total	***N=557***					

Source: Page 58 of the report for Study 3203-005, Table 12 on page 50 of the report for Study 3203-008, Table 18

on page 67 of the report for Study 3203-009, and Table 1 on page 5 of the submission dated June 13, 2006.

Disposition

In the Phase 2/3 oxymorphone ER trials, 64% of the 1828 patients discontinued early with adverse events being the most common cause (35%). Across the oxymorphone IR trials, 42% of the 557 patients in oxymorphone IR Phase 2/3 trials discontinued early. Lack of efficacy (24%) was the most common reason for early discontinuation. This is comparable to the experience with the patients who received oxycodone IR in these trials: 34% of the 278 patients treated discontinued early, 22% due to lack of efficacy.

SAFETY

Deaths

There were a total of 49 deaths in the oxymorphone development program. Thirty five of these deaths were reviewed during the original application. Thirty four of these deaths occurred in patients with cancer pain. Dr. Fang has performed a detailed review of the deaths, reviewing each of the narratives. Thirteen of the deaths reported in this submission were reported from open-label studies, EN3202-021, 028, and 029. These were cancer patients who had been on oxymorphone treatment for a period ranging from two weeks to 10 weeks prior to the death. There does not appear to be a causative relationship between these deaths and study drug. The remaining death was a 73-year old woman with chronic low back pain and a history of hypertension, diabetes mellitus, hyperlipidemia, Parkinson's disease, prior myocardial infarction, and breast cancer. The patient had several episodes of pneumonia and sinus infection after starting Study EN3202-032 while titrating on to oxymorphone ER with oxymorphone IR as rescue. The patient had previously been treated with OxyContin. It is unlikely that the patient's pneumonia and subsequent death was related to use of study medication.

Serious Adverse Events

The nature of the serious adverse events during clinical trials with oxymorphone ER did not change appreciably from the original application. The overall incidence was comparable and the individual event frequencies did not change substantially. The four cases of drug interaction NOS were oxymorphone overdoses in the original application in the postoperative setting where PCA oxymorphone was also part of the acute postoperative treatment for pain. No further cases of overdose were reported.

Table 18. Number (%) of Oxymorphone ER-treated Patients with Non-Fatal SAEs in Descending Frequency in Phase 2/3 ER Trials

	120-Day Safety	Update	Overall
Total # patients treated with oxymorphone ER	(N = 1089)	(N = 972) [a]	(N = 2011) [b]
MedDRA preferred term			
Any adverse events	93 (8.5)	62(6.4)	150 (**7.5**)
Chest pain NEC	7 (0.6)	4 (0.4)	11 (**0.5**)
Pneumonia NOS	3 (0.3)	8 (0.8)	11 (**0.5**)
Vomiting NOS	8 (0.7)	3 (0.3)	10 (**0.5**)
Dehydration	5 (0.5)	4 (0.4)	9 (0.4)
Nausea	6 (0.6)	4 (0.4)	9 (0.4)
Dyspnea NOS	5 (0.5)	1 (0.1)	6 (0.3)
Abdominal pain NOS	4 (0.4)	2 (0.2)	5 (0.2)
Back pain	3 (0.3)	1 (0.1)	4 (0.2)
Confusional state	0 (0.0)	4 (0.4)	4 (0.2)
Drug interaction NOS	4 (0.4)	0 (0.0)	4 (0.2)
Hypotension NOS	3 (0.3)	1 (0.1)	4 (0.2)
Osteoarthritis aggravated	4 (0.4)	0 (0-0)	4 (0.2)
Pulmonary embolism	2 (0.2)	2 (0.2)	4 (0.2)
Pyrexia	2 (0.2)	2 (0.2)	4 (0.2)
Urinary retention	3 (0.3)	1 (0.1)	4 (0.2)
Atrial fibrillation	3 (0.3)	0 (0.0)	3 (0.1)
Cholelithiasis	1 (0.1)	2 (0.2)	3 (0.1)
Chronic obstructive airways disease exacerbated	2 (0.2)	1 (0.1)	3 (0.1)
Concomitant disease progression	2 (0.2)	1 (0.1)	3 (0.1)
Depressed level of consciousness	3 (0.3)	0 (0.0)	3 (0.1)
Malignant pleural effusion	1 (0.1)	2 (0.2)	3 (0.1)
Pain exacerbated	2 0.2)	1 (0.1)	3 (0.1)
Pain in limb	3 (0.3)	0 (0.0)	3 (0.1)
Pain NOS	1 (0.1)	2 (0.2)	3 (0.1)
Urinary tract infection NOS	3 (0.3)	0 (0.0)	3 (0.1)
Venous thrombosis deep limb	3 (0.3)	0 (0.0)	3 (0.1)
Chest pain aggravated	0 (0.0)	2 (0.2)	2 (0.1)
Drug withdrawal syndrome	0 (0.0)	2 (0.2)	2 (0.1)
Hypoxia	0 (0.0)	2 (0.2)	2 (0.1)
Intractable pain	0 (0.0)	2 (0.2)	2 (0.1)
Malignant neoplasm progression	0 (0.0)	2 (0.2)	2 (0.1)
Mental status changes	0 (0.0)	2 (0.2)	2 (0.1)
Obstructive uropathy	0 (0.0)	2 (0.2)	2 (0.1)
Renal failure NOS	0 (0.0)	2 (0.2)	2 (0.1)
Respiratory failure	0 (0.0)	2 (0.2)	2 (0.1)
Syncope	0 (0.0)	2 (0.2)	2 (0.1)

[a] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
[b] Overall column includes all serious AEs, some of which may not be classified as serious before the 120-Day Safety cutoff date but later became serious.
Source: Applicant Table 16 on page 171-179, safety.pdf

The serious adverse events in the oxymorphone IR trials were also less frequent in the new data compared to the original safety database.

Table 19. Number (%) of Oxymorphone IR-Treated Patients with Non-Fatal SAEs in Descending Frequency in Phase 2/3 IR Trials

	ISS	Update	Overall
Total # patients treated with oxymorphone ER	(N = 334)	(N = 223) [a]	(N = 557)
MedDRA preferred term			
Any adverse events	18 (5.4)	7 (3.1)	25 (4.5)
Myocardial infarction	3 (0.9)	0 (0.0)	3 (0.5)
Venous thrombosis deep limb	3 (0.9)	0 (0.0)	3 (0.5)
Coma NEC	2 (0.6)	0 (0.0)	2 (0.4)
Ileus	2 (0.6)	0 (0.0)	2 (0.4)
Pneumonia NOS	1 (0.3)	1 (0.4)	2 (0.4)
Pyrexia	1 (0.3)	1 (0.4)	2 (0.4)
Adult respiratory distress syndrome	1 (0.3)	0 (0.0)	1 (0.2)
Cardiogenic shock	1 (0.3)	0 (0.0)	1 (0.2)
Chest pain NEC	0 (0.0)	1 (0.4)	1 (0.2)
Confusion	1 (0.3)	0 (0.0)	1 (0.2)
Depressed level of consciousness	1 (0.3)	0 (0.0)	1 (0.2)
Disorientation	1 (0.3)	0 (0.0)	1 (0.2)
Dyspnea NOS	1 (0.3)	0 (0.0)	1 (0.2)
Hypotension NOS	1 (0.3)	0 (0.0)	1 (0.2)
Hypoventilation	1 (0.3)	0 (0.0)	1 (0.2)
Hypoxia	1 (0.3)	0 (0.0)	1 (0.2)
Leukocytosis	0 (0.0)	1 (0.4)	1 (0.2)
Mental status changes	1 (0.3)	0 (0.0)	1 (0.2)
Muscle contractions involuntary	1 (0.3)	0 (0.0)	1 (0.2)
Nausea	0 (0.0)	1 (0.4)	1 (0.2)
Pneumothorax NOS	1 (0.3)	0 (0.0)	1 (0.2)
Postoperative ileus	0 (0.0)	1 (0.4)	1 (0.2)
Radius fracture	1 (0.3)	0 (0.0)	1 (0.2)
Renal failure acute	1 (0.3)	0 (0.0)	1 (0.2)
Respiratory distress	1 (0.3)	0 (0.0)	1 (0.2)
Small intestinal obstruction NOS	0 (0.0)	1 (0.4)	1 (0.2)
Somnolence	1 (0.3)	0 (0.0)	1 (0.2)
Sweating increased	1 (0.3)	0 (0.0)	1 (0.2)
Tachycardia NOS	0 (0.0)	1 (0.4)	1 (0.2)
Tendon rupture	1 (0.3)	0 (0.0)	1 (0.2)
Tremor NEC	1 (0.3)	0 (0.0)	1 (0.2)
Uterine cancer NOS	0 (0.0)	1 (0.4)	1 (0.2)
Vaginal cellulitis	0 (0.0)	1 (0.4)	1 (0.2)
Vomiting NOS	0 (0.0)	1 (0.4)	1 (0.2)
Wound infection NEC	1 (0.3)	0 (0.0)	1 (0.2)

[a] New Subjects since the ISS.
Source: Table 17 on pages 180-181 of the update safety report.

Dr. Fang did a thorough review of cardiac serious adverse events and did not find any potential causal relationship or safety signal of concern. Her thorough review of QTc data found that

these events were not apparently drug related as most resolved while on oxymorphone or after rechallenge.

Discontinuation Due to Adverse Events

The frequency of discontinuation due to adverse events was lower in the new data (26%) than in the original application (36%). Dr. Fang notes that this may be due to the study design in which patients titrated onto study drug in Studies EN3202-031 and 032 which may have improved tolerability.

Table 20. Number (%) of Oxymorphone ER-treated Patients with AEs Causing Dropouts in Descending Frequency in Phase 2/3 ER trials

	120-Day Safety	Update	Overall
Total # patients treated with oxymorphone ER	(N = 1089)	(N = 972) [a]	(N = 2011) [b]
MedDRA preferred term			
Any adverse events	391 (35.9)	251 (25.8)	642 (31.9)
Nausea	157 (14.4)	59 (6.1)	216 (10.7)
Dizziness (exc vertigo)	93 (8.5)	32 (3.3)	124 (6.2)
Vomiting NOS	85 (7.8)	23 (2.4)	108 (5.4)
Somnolence	43 (3.9)	29 (3.0)	72 (3.6)
Constipation	45 (4.1)	26 (2.7)	71 (3.5)
Pruritus NOS	39 (3.6)	18 (1.9)	57 (2.8)
Headache NOS	26 (2.4)	16 (1.6)	42 (2.1)
Sweating increased	27 (2.5)	10 (1.0)	37 (1.8)
Sedation	26 (2.4)	6 (0.6)	32 (1.6)
Fatigue	16 (1.5)	12 (1.2)	28 (1.4)
Insomnia NOS	10 (0.9)	9 (0.9)	19 (0.9)
Abdominal pain NOS	10 (0.9)	8 (0.8)	18 (0 .9)
Diarrhea NOS	11 (1.0)	6 (0.6)	17 (0.8)
Dry mouth	13 (1.2)	4 (0.4)	17 (0.8)
Lethargy	8 (0.7)	8 (0.8)	16 (0.8)
Concomitant disease progression	(0.8)	2 (0.2)	14 (0.7)
Confusion	(1.2)	0 (0.0)	14 (0.7)
Anxiety NEC	6 (0.6)	6 (0.6)	12 (0.6)
Dyspnea NOS	6 (0.6)	5 (0.5)	11 (0.5)
Nervousness	5 (0.5)	6 (0.6)	11 (0.5)
Appetite decreased NOS	7 (0.6)	3 (0.3)	10 (0.5)
Disorientation	7 (0.6)	3 (0.3)	10 (0.5)

[a] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
[b] Overall column includes all AEs causing study drug discontinuation, some of which may not be included in the other two columns since these AEs existed before the 120-Day Safety Update, but the subject later discontinued without the AE worsening in severity.
Source: Table 18 on page 184 to 196.

The adverse events leading to study discontinuation were very similar in the new data as compared to the original submission.

Table 21. Number (%) of Oxymorphone IR-Treated Patients with AEs Causing Dropouts in Descending Frequency in Phase 2/3 IR Trials

	120-Day Safety	Update	Overall
Total # patients treated with oxymorphone IR	(N = 334)	(N = 223) [a]	(N = 557)
MedDRA preferred term			
Any adverse events	34 (10.2)	21 (9.4)	55 (9.9)
Nausea	6 (1.8)	8 (3.6)	14 (2.5)
Vomiting NOS	6 (1.8)	6 (2.7)	12 (2.2)
Sedation	4 (1.2)	2 (0.9)	6 (1.1)
Somnolence	5 (1.5)	1 (0.4)	6 (1.1)
Headache NOS	1 (0.3)	3 (1.3)	4 (0.7)
Coma NEC	3 (0.9)	0 (0.0)	3 (0.5)
Confusion	3 (0.9)	0 (0.0)	3 (0.5)
Respiratory depression	3 (0.9)	0 (0.0)	3 (0.5)
Abdominal pain NOS	1 (0.3)	1 (0.4)	2 (0.4)
Agitation	1 (0.3)	0 (0.0)	1 (0.2)
Confusional state	0 (0.0)	1 (0.4)	1 (0.2)
Constipation	1 (0.3)	0 (0.0)	1 (0.2)
Depressed level of consciousness	1 (0.3)	0 (0.0)	1 (0.2)
Disorientation	1 (0.3)	0 (0.0)	1 (0.2)
Dyspnea NOS	1 (0.3)	0 (0.0)	1 (0.2)
Feeling abnormal	1 (0.3)	0 (0.0)	1 (0.2)
Hallucination NOS	1 (0.3)	0 (0.0)	1 (0.2)
Headache NOS aggravated	1 (0.3)	0 (0.0)	1 (0.2)
Hypotension NOS	1 (0.3)	0 (0.0)	1 (0.2)
Hypoventilation	1 (0.3)	0 (0.0)	1 (0.2)
Hypoxia	1 (0.3)	0 (0.0)	1 (0.2)
Ileus	1 (0.3)	0 (0.0)	1 (0.2)
Incision site complication	0 (0.0)	1 (0.4)	1 (0.2)
Lethargy	1 (0.3)	0 (0.0)	1 (0.2)
Mental status changes	1 (0.3)	0 (0.0)	1 (0.2)
Migraine NOS	0 (0.0)	1 (0.4)	1 (0.2)
Myocardial infarction	1 (0.3)	0 (0.0)	1 (0.2)
Pruritus NOS	0 (0.0)	1 (0.4)	1 (0.2)
Rash NOS	0 (0.0)	1 (0.4)	1 (0.2)
Respiratory distress	1 (0.3)	0 (0.0)	1 (0.2)
Sweating increased	1 (0.3)	0 (0.0)	1 (0.2)
Tachycardia NOS	0 (0.0)	1 (0.4)	1 (0.2)

[a] New Subjects since the ISS.
Source: Table 19 on pages 197 to 198 of the update safety report.

Adverse Events

The most common adverse events are for the most part consistent with known opioid adverse events and did not change appreciably in the current data when compared to the original database. The overall rate of adverse events, 85% in the oxymorphone ER group compared to 57% in the placebo group. Due to the availability of rescue medication in the clinical trials, the placebo patients also experienced some opioid-related adverse events however limits placed on rescue is several studies would limit the adverse events as well.

Table 22. The Most Frequent (≥5%) AEs Reported in All (Controlled and Open-Label) Phase 2/3 ER Trials

Treatment group	Oxymorphone ER			Placebo		
Database	120-Day	Update [a]	Overall	120-Day	Update [a]	Overall
Total # patients	(N = 1089)	(N = 972)	(N = 2011)	(N = 350)	(N = 172)	(N = 522)
MedDRA preferred term						
Any adverse experience	976 (89.6)	759 (78.1)	1702 (84.6)	225 (64.3)	71 (41.3)	296 (56.7)
Nausea	500 (45.9)	213 (21.9)	711 (35.4)	63 (18.0)	10 (5.8)	73 (14.0)
Constipation	435 (39.9)	236 (24.3)	670 (33.3)	63 (18.0)	2 (1.2)	65 (12.5)
Dizziness (exc vertigo)	280 (25.7)	111 (11.4)	388 (19.3)	35 (10.0)	3 (1.7)	38 (7.3)
Vomiting NOS	256 (23.5)	91 (9.4)	346 (17.2)	23 (6.6)	2 (1.2)	25 (4.8)
Pruritus NOS	264 (24.2)	75 (7.7)	339 (16.9)	42 (12.0)	1 (0.6)	43 (8.2)
Somnolence	179 (16.4)	154 (15.8)	333 (16.6)	14 (4.0)	0 (0.0)	14 (2.7)
Headache NOS	129 (11.8)	104 (10.7)	233 (11.6)	26 (7.4)	2 (1.2)	28 (5.4)
Sweating increased	200 (18.4)	34 (3.5)	232 (11.5)	37 (10.6)	4 (2.3)	41 (7.9)
Sedation	188 (17.3)	14 (1.4)	202 (10.0)	37 (10.6)	0 (0.0)	37 (7.1)
Dry mouth	81 (7.4)	44 (4.5)	125 (6.2)	1 (0.3)	2 (1.2)	3 (0.6)
Insomnia NEC	62 (5.7)	55 (5.7)	117 (5.8)	8 (2.3)	2 (1.2)	10 (1.9)
Diarrhea NOS	68 (6.2)	47 (4.8)	115 (5.7)	18 (5.1)	8 (4.7)	26 (5.0)
Fatigue	60 (5.5)	51 (5.2)	111 (5.5)	4 (1.1)	2 (1.2)	6 (1.1)
Appetite decreased NOS	54 (5.0)	24 (2.5)	78 (3.9)	1 (0.3)	1 (0.6)	2 (0.4)

[a] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
Note: AEs included in this table occurred in ≥5% of subjects in either column. This table is sorted by Overall Total frequency in descending order.
Source: Table 26 on pages 383 to 422.

The common adverse events were also very similar but less frequent in the updated data compared to the original data. The comparison to oxycodone IR is helpful in putting the adverse event profile of oxymorphone IR in context. There are no trends for more frequent events with oxymorphone IR as compared to oxycodone IR and for some

Table 23. The Most Frequent (≥1.5%) AEs Reported in All Phase 2/3 Oxymorphone IR Trials

	Oxymorphone IR			Oxycodone IR			Placebo		
Database	ISS	Update	Overall	ISS	Update	Overall	ISS	Update	Overall
#treated	N=334	N=223	N=557	N=195	N=83	N=278	N=123	N=147	N=270
Any AE	237 (71.0)	112 (50.2)	349 (62.7)	126 (64.6)	45 (54.2)	171 (61.5)	57 (46.3)	57 (38.8)	114 (42.2)
Nausea	55 (16.5)	51 (22.9)	106 (19.0)	38 (19.5)	23 (27.7)	61 (21.9)	8 (6.5)	23 (15.6)	31 (11.5)
Pyrexia	73 (21.9)	6 (2.7)	79 (14.2)	31 (15.9)	4 (4.8)	35 (12.6)	19 (15.4)	3 (2.0)	22 (8.1)
Somnolence	49 (14.7)	3 (1.3)	52 (9.3)	27 (13.8)	2 (2.4)	29 (10.4)	5 (4.1)	1 (0.7)	6 (2.2)
Vomiting NOS	26 (7.8)	24 (10.8)	50 (9.0)	13 (6.7)	8 (9.6)	21 (7.6)	5 (4.1)	14 (9.5)	19 (7.0)
Pruritus NOS	26 (7.8)	18 (8.1)	44 (7.9)	12 (6.2)	11 (13.3)	23 (8.3)	4 (3.3)	6 (4.1)	10 (3.7)
Headache NOS	10 (3.0)	28 (12.6)	38 (6.8)	8 (4.1)	6 (7.2)	14 (5.0)	1 (0.8)	11 (7.5)	12 (4.4)
Dizziness	28 (8.4)	8 (3.6)	36 (6.5)	10 (5.1)	7 (8.4)	17 (6.1)	2 (1.6)	4 (2.7)	6 (2.2)
Constipation	17 (5.1)	6 (2.7)	23 (4 .1)	14 (7.2)	2 (2.4)	16 (5.8)	1 (0.8)	2 (1.4)	3 (1.1)
Confusion	15 (4.5)	0 (0.0)	15 (2.7)	5 (2.6)	0 (0.0)	5 (1.8)	2 (1.6)	0 (0.0)	2 (0.7)
Anemia NOS	13 (3.9)	1 (0.4)	14 (2.5)	4 (2.1)	0 (0.0)	4 (1.4)	4 (3.3)	0 (0.0)	4 (1.5)
Dry mouth	8 (2.4)	2 (0.9)	10 (1.8)	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.4)	2 (0.7)
Tachycardia	7 (2 .1)	3 (1.3)	10 (1 .8)	1 (0.5)	0 (0.0)	1 (0.4)	2 (1.6)	0 (0.0)	2 (0.7)
Hypoxia	8 (2.4)	1 (0.4)	9 (1.6)	8 (4.1)	1 (1.2)	9 (3.2)	5 (4.1)	1 (0.7)	6 (2.2)

Note: The 28 patients who received both placebo and oxymorphone treatments were counted in both groups. Source: Table 27 on pages 423 to 435 of the update safety report.

Laboratory Findings

Dr. Fang reviewed the changes in white blood cell count noted in the prior review of safety. She found that there were no consistent findings that could be attributed to study drug, but in fact many were due to laboratory sample mishandling. Several repeated tests were normal.

Adverse Events of Interest

Patients Requiring Opioid Antagonists

A total of 27 subjects in the original ISS received naloxone. Twenty-three of the 27 subjects requiring naloxone were enrolled in one of the three acute post-operative pain trials (EN3202-012, EN3203-004, and EN 3203-005). The rates of naloxone use are detailed in Table 18. The incidence of use of naloxone in postsurgical patients receiving oxymorphone ER was 6.2%.

Table 18 Incidence of Naloxone Use in Acute Post-Operative Pain Trials

Study Group			
EN3202-012	Oxymorphone ER	Placebo	
	N=65	N=61	
	4 (6.1%)	0 (0.0%)	
EN3203-004 and EN3203-005	Oxymorphone IR	Oxycodone IR	Placebo
	N=334	N=123	N=195
	12 (3.6%)	1 (0.5%)	0

The four subjects in the oxymorphone ER group from the preceding table had an adverse event coded to the term "drug interaction NOS", but these were actually overdoses. Each of these events occurred following use of a single dose of oxymorphone ER and several doses of PCA hydromorphone. One of these patient had received a 60 mg dose of oxymorphone ER as well.

In the current update, there were four cases of hypoxia identified in the oxymorphone ER patient groups. Two of these were serious. The narratives of these were reviewed with all of the serious adverse events. Patient 212-012 was a 44 year old man with metastatic lung cancer. He began treatment with oxymorphone in March of 2004 and had progressive symptoms including hypoxia on room air (88%) in [redacted]. He was found to have a large pleural effusion. There is no evidence that the hypoxia was related to oxymorphone. Patient 127-004 was a 63 year old woman with neuropathic pain. She began oxymorphone in December of 2003. In [redacted] the patient developed pneumonia with hypoxia (92%) that resolved with treatment. There is no evidence of a casual relationship between study medication and hypoxia in this patient. One case of hypoxia in study EN3202-032 was not considered serious, but the patient received naloxone in the setting of a tooth extraction at which time also receiving Vicodin. The dose of oxymorphone ER was not documented at that time. It is impossible to know whether there was a causal relationship between the oxymorphone and the event independent of effects of Vicodin.

Drug-Drug Interactions

No major clinically significant drug-drug interactions were noted in the clinical trials.

Withdrawal Effects

In the initial application, there were six oxymorphone ER-treated subjects and two oxycodone ER-treated subjects with adverse events mapped to drug withdrawal syndrome. Two of these events occurred in Study EN3202-016, in which subjects were re-randomized to placebo treatment after stabilization on double-blind treatment with oxymorphone ER or oxycodone ER.

In the update, there were five patients with symptoms of opioid withdrawal in Study EN3202-032 after randomization to placebo. These were opioid tolerant patients and the available rescue medication was insufficient to avoid withdrawal symptoms. There were also three patients in Study EN3202-031, two after randomization to placebo, one while on treatment with oxymorphone.

As an opioid, the potential for opioid withdrawal is not surprising and patients who are opioid tolerant will need adequate taper if they are to be taken off oxymorphone. Care in conversion to other opioids will also need to be taken in order to avoid withdrawal symptoms as well as toxicity.

Overdose

As described in the original review of safety, there was one accidental overdose by a patient who mistakenly took four tablets instead of one, for one dose. The subject contacted the study site and was monitored. No adverse events were noted. Several cases of patients requiring naloxone for oversedation or respiratory depression in the postoperative setting have been described.

There were no reports of overdose in the updated data in the current submission.

Drug Abuse and Abuse Liability

Oxymorphone is a mu-agonist opioid analgesic and it's abuse liability can be expected to be similar to morphine. Data from the clinical trials suggest that withdrawal will occur with abrupt discontinuation. There were two episodes of drug diversion at two clinical sites during the clinical development program as described in the original review. There were no new reports of diversion in the updated data.

The Controlled Substances Staff provided a consultation. It appears that the recommendations were based on a review of the original NDA submission which identified problems with proposed dosing for the oxymorphone IR formulation and which found safety concerns with the oxymorphone ER product in the postoperative period. This review addresses those concerns.

The CSS consult made the following recommendations:

1. Medication Guide

   CSS states that the potency and dosage strengths for this product mandate a Med Guide for the ER formulation and a PPI for the IR formulation. The relative potency of oxymorphone compared to other opioids is not well defined and may differ in the setting of opioid tolerance, but CSS notes relative potencies of approximately 0.333 for morphine and 1.33 for hydromorphone. The same source suggests a relative potency of 0.5 for oxycodone. The proposed strengths for the oxymorphone ER formulation, 5, 10, 20,and 40 mg. However, oxymorphone ER and IR has not been found to have any greater evidence of toxicity in this safety database when compared to oxycodone ER and IR. The oral bioavailability of oxymorphone ER and IR is only 10%, in contrast to 60-80% for oxycodone ER which is available in dosage strengths up to 80 mg (160 mg is approved, not currently marketed). The oral bioavailability for morphine ER is approximately 40 % and these are available in dosage strengths up to 100 mg. So while relative potency of the actual drug substance of oxymorphone may be greater than for morphine or oxycodone, the limited bioavailability substantially reduces the relative potency of the drug product.

   The only modified-release oral opioid approved with a Medication Guide is Palladone. All strengths of Palladone are indicated only for opioid tolerant patients due to the amount high potency hydromorphone. Oxymorphone ER has been safely titrated and used in opioid naïve patients as demonstrated in Study EN3202-031.

Therefore, I disagree that a Medication Guide is indicated for this oxymorphone ER.

Similarly, reducing the dose of oxymorphone IR to no more than 20 mg in the postoperative period eliminated the serious adverse events and provided a safety profile comparable to oxycodone IR. Therefore I do not agree that a PPI is indicated for oxymorphone IR when it is not indicated for oxycodone IR.

2. The labeling should be revised to include more clearly the risks of prescribing the ER dosage form to non-opioid tolerant patients.

I agree that this is extremely important. The following language is in the current package insert for oxymorphone ER.

> Initiation of Therapy
> Opioid-Naïve Patients
> It is suggested that patients who are not opioid-experienced being initiated on chronic around-the-clock opioid therapy be started with OPANA ER 5 mg every 12 hours. Thereafter, it is recommended that the dose be individually titrated, preferably at increments of 5-10 mg every 12 hours every 3-7 days, to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician (see **CLINICAL TRIALS: 12-Week Study in Opioid-Naïve Patients with Low Back Pain**)

3. The labeling should address the safety issues of high potency and high rate of adverse effects associate with oxymorphone.

The adverse event profile for the two formulations of oxymorphone were comparable to the adverse events with oxycodone treatment arms in the same studies.

4. Revise the information provided to assist in conversion form other oral opioid to proposed products to a more user friendly, less confusion format with sources(s) for data cited.

The current conversion table represents the conversion used in clinical trials and is intended to be a conversion guide and not an equianalgesic table. Based on the clinical trials, patients converting from other opioids did not need to titrate down after this conversion. To ensure greater safety across broad use, the package insert recommends calculating the conversion, halving the dose and then titrating as needed.

> This following is from the package insert:
> **Conversion from Other Oral Opioids to OPANA ER**
> For conversion from other opioids to OPANA ER, physicians and other health care professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start the OPANA therapy by administering half of the calculated total daily dose of OPANA ER (see conversion ratio table below) in 2 divided doses, every 12 hours. The initial dose of OPANA ER can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved. , the following table provides approximate equivalent doses, which may be used as a

guideline. In a Phase 3 clinical trial with an open-label titration period, patients were converted from their current opioid to OPANA ER using the following table as a guide. In general, patients were able to successfully titrate to a stabilized dose of OPANA ER within 4 weeks (see **CLINICAL TRIALS: 12-Week Study in Opioid-Experienced Patients with Low Back**). There is substantial patient variation in the relative potency of different opioid drugs and formulations.

CONVERSION RATIOS TO OPANA ER

Opioid	Approximate Equivalent Dose Oral	Oral Conversion Ratio[a]
Oxymorphone	10 mg	1
Hydrocodone	20 mg	0.5
Oxycodone	20 mg	0.5
Methadone	20 mg	0.5
Morphine	30 mg	0.333

[a]Ratio for conversion of oral opioid dose to approximate oxymorphone equivalent dose. Select opioid and multiply the dose by the conversion ratio to calculate the approximate oral oxymorphone equivalent.

- Sum the total daily dose for the opioid and multiply by the conversion ratio to calculate the oxymorphone total daily dose.
- For patients on a regimen of mixed opioids, calculate the approximate oral oxymorphone dose for each opioid and sum the totals to estimate the total daily oxymorphone dose.
- The dose of OPANA ER can be gradually adjusted, preferably at increments of 10 mg every 12 hours every 3-7 days, until adequate pain relief and acceptable side effects have been achieved (see Individualization of Dose).

5. The sponsor should provide more details on the DrugLogic proportional analysis engine data and how it will be used to manage risk in the post-marketing surveillance plan for the proposed product.

This comment has been forward to the Applicant. The risk minimization plan has been reviewed the Office of Safety and Epidemiology and has been found to be acceptable.

SPECIAL POPULATIONS

There were too few non Caucasian subjects to adequately explore the effects of race and ethnicity on efficacy. Among oxymorphone ER-treated subjects in the Phase 2/3 ER trials, the incidence of dizziness, somnolence, and headache were slightly higher in Caucasians compared to Blacks, but the relatively small proportion of Blacks (8%) makes the clinical significance of this difference uncertain.

There were too few subjects over the age of 65 years to provide a meaningful evaluation of the effects of age on efficacy in the only trial supporting the proposed indication, EN3202-016. The frequency of some adverse events, such as somnolence and dizziness, may increase with increasing age in oxymorphone ER-treated subjects..

OPANA ER should be used with caution in elderly patients. The plasma levels of oxymorphone are about 40% higher in elderly (≥65 years of age) than in younger subjects (see **CLINICAL PHARMACOLOGY**). Elderly patients should initially receive smaller starting doses of oxymorphone and dose titration should proceed cautiously.

Of the total number of subjects in clinical studies of oxymorphone ER, 27 percent were 65 and over, while 9 percent were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, confusion, and nausea.

Of the total number of subjects in clinical studies of oxymorphone IR, 31 percent were 65 and over, while 7 percent were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, confusion, and nausea. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

There were no consistent effects of gender on efficacy. Nausea, vomiting, and headache were notably more frequently in females (48.9%, 28.0%, and 14.6%, respectively), compared to males (35.9%, 13.9%, and 7.0%, respectively). This gender difference was not seen in placebo-treated subjects

There will be a postmarketing commitment to fulfill the requirements of PREA.

DOSING

The clinical pharmacokinetic and bioavailability studies were also conducted. A dosing interval of every 12 hours has been utilized in the Study EN3203-016 in which efficacy was demonstrated and is supported by the pharmacokinetic profile of oxymorphone extended-release tablets.

Dose adjustments are called for in mild hepatic impairment, titration should begin low and proceed with close clinical monitoring. Oxymorphone is highly metabolized by the liver. Use of oxymorphone should be contraindicated in moderate and severe hepatic impairment. As oxymorphone plasma concentrations were relatively higher in the setting of renal impairment, dosing of oxymorphone should be started at low doses and titrated carefully in all categories of renal impairment under close clinical supervision. Patients over age of 65 exhibited higher plasma concentrations, AUC and Cmax. Therefore, dosing in patients over the age of 65 should begin with low starting doses and titrated carefully under close clinical supervision.

The following is from the Dosage and Administration section from the package insert: Oxymorphone ER (OPANA ER)

Initiation of Therapy
Opioid-Naïve Patients
It is suggested that patients who are not opioid-experienced being initiated on chronic around-the-clock opioid therapy be started with OPANA ER 5 mg every 12 hours. Thereafter, it is recommended that the dose be individually titrated, preferably at increments of 5-10 mg every 12 hours every 3-7 days, to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician (see **CLINICAL TRIALS: 12-Week Study in Opioid-Naïve Patients with Low Back Pain**)

Opioid-Experienced Patients
Conversion from OPANA to OPANA ER
Patients receiving OPANA (IR) may be converted to OPANA ER by administering half the patient's total daily oral OPANA (IR) dose as OPANA ER, every 12 hours. For example, a patient receiving 40 mg/day OPANA (IR) may require 20 mg OPANA ER every 12 hours.

Conversion from Parenteral Oxymorphone to OPANA ER
Given the absolute oral bioavailability of approximately 10%, patients receiving parenteral oxymorphone may be converted to OPANA ER by administering 10 times the patient's total daily parenteral oxymorphone dose as OPANA ER in two equally divided doses (e.g., IV dose x 10/2). For example, approximately 20 mg of OPANA ER, every 12 hours, may be required to provide pain relief equivalent to a total daily dose of 4 mg of parenteral oxymorphone. Due to patient variability with regards to opioid analgesic response, upon conversion patients should be closely monitored to ensure adequate analgesia and to minimize side effects.

Conversion from Other Oral Opioids to OPANA ER
For conversion from other opioids to OPANA ER, physicians and other health care professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start the OPANA therapy by administering half of the calculated total daily dose of OPANA ER (see conversion ratio table below) in 2 divided doses, every 12 hours. The initial dose of OPANA ER can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved. , the following table provides approximate equivalent doses, which may be used as a guideline. In a Phase 3 clinical trial with an open-label titration period, patients were converted from their current opioid to OPANA ER using the following table as a guide. In general, patients were able to successfully titrate to a stabilized dose of OPANA ER within 4 weeks (see **CLINICAL TRIALS: 12-Week Study in Opioid-Experienced Patients with Low Back**). There is substantial patient variation in the relative potency of different opioid drugs and formulations.

CONVERSION RATIOS TO OPANA ER

Opioid	Approximate Equivalent Dose Oral	Oral Conversion Ratio[a]
Oxymorphone	10 mg	1
Hydrocodone	20 mg	0.5
Oxycodone	20 mg	0.5
Methadone	20 mg	0.5
Morphine	30 mg	0.333

[a]Ratio for conversion of oral opioid dose to approximate oxymorphone equivalent dose. Select opioid and multiply the dose by the conversion ratio to calculate the approximate oral oxymorphone equivalent.

- Sum the total daily dose for the opioid and multiply by the conversion ratio to calculate the oxymorphone total daily dose.
- For patients on a regimen of mixed opioids, calculate the approximate oral oxymorphone dose for each opioid and sum the totals to estimate the total daily oxymorphone dose.
- The dose of OPANA ER can be gradually adjusted, preferably at increments of 10 mg every 12 hours every 3-7 days, until adequate pain relief and acceptable side effects have been achieved (see Individualization of Dose).

Oxymorphone IR (OPANA)

Initiation of Therapy
Opioid-Naïve Patients
Patients who have not been receiving opioid analgesics should be started on OPANA in a dosing range of 10 to 20 mg every four to six hours depending on the initial pain intensity. If deemed necessary to initiate therapy at a lower dose, patients may be started with OPANA 5 mg. The dose should be titrated based upon the individual patient's response to their initial dose of OPANA. This dose can then be adjusted to an acceptable level of analgesia taking into account the pain intensity and side effects experienced by the patient.

Initiation of therapy with doses higher than 20 mg is not recommended because of potential serious side effects (see CLINICAL TRIALS: Orthopedic Surgery).

Conversion from Parenteral Oxymorphone to OPANA
Given the absolute oral bioavailability of approximately 10%, patients receiving parenteral oxymorphone may be converted to OPANA by administering 10 times the patient's total daily parenteral oxymorphone dose as OPANA, in four or six equally divided doses (e.g. IV dose x 10/4). For example, approximately 10 mg of OPANA may be required to provide pain relief equivalent to a total daily IM dose of 4 mg oxymorphone. The dose can be titrated to optimal pain relief or combined with acetaminophen/NSAIDs for optimal pain relief. Due to patient variability with regard to opioid analgesic response, upon conversion patients should be closely monitored to ensure adequate analgesia and to minimize side effects.

Conversion from Other Oral Opioids to OPANA

For conversion from other opioids to OPANA, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start the OPANA therapy by administering half of the calculated total daily dose of OPANA in 4 to 6 equally divided doses, every 4-6 hours. The initial dose of OPANA can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved.

Additional comments

Dr. Fang suggest that the Applicant enter into a postmarketing commitment to study the relative potency of oxymorphone and other opioids. As a safe conversion method from other opioids has been described, this can be left up to the Applicant's discretion.

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/s/

Sharon Hertz
6/22/2006 07:01:44 PM
MEDICAL OFFICER

2nd Cycle

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-610
Submission Code	N000
Letter Date	12-22-05, 3-28-06, 4-3-06, 5-23-06, 5-26-06, 6-2-06
PDUFA Goal Date	June 22, 2006
Reviewer Name	Christina Fang, M.D.
Review Completion Date	June 22, 2006
Established Name	Oxymorphone Extended-Release Tablets
(Proposed) Trade Name	OPANA™ ER
Therapeutic Class	Opioid analgesics
Applicant	Endo Pharmaceuticals Inc.
Priority Designation	3S
Formulation	Extended-release tablets, 5, 10, 20, and 40 mg
Dosing Regimen	Individualized
Indication	Moderate to severe chronic pain
Intended Population	Adult patients requiring continuous, around-the-clock opioid therapy for an extended period of time

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Oxymorphone ER (extended-release) is recommended for approval for the relief of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid.

The recommendation for approval is based on the acceptable benefit/risk ratio determined from the evaluation of efficacy and safety data submitted in NDA 21-610.

Oxymorphone ER studied at individualized dosage in highly selected responders was shown to be efficacious in treating chronic low back pain based on the replicable positive findings from the studies of chronic low back pain.

Oxymorphone ER has a similar safety profile as the other opioid drugs and is considered reasonably safe to be used with a careful initial dose titration to meet individual's acceptance of tolerance, for the treatment of chronic pain in both opioid naïve and opioid experienced populations.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

The Sponsor's proposed post-marketing Risk Management Plan (RMP) for oxymorphone products is considered acceptable in general. The additional recommendations from the Office of Drug Safety and the Controlled Substance Staff will be forwarded to the Sponsor.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

There should be further studies of relative potency in comparison to the other commonly used opioids to well inform the labeling.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The original submission of NDA 21-610 had twelve Phase 1 studies and ten Phase 2/3 studies, all reviewed in detail before an approvable regulatory action was granted by the Division in October 2003. There are four new Phase 2/3 studies in the current submission, including two efficacy studies of chronic low back pain (Studies 031 and 032) and two open-label safety studies of chronic pain (Studies 028 and 029).

1.3.2 Efficacy

The two studies (031 and 032) had a very similar design. They were studies of open-label, titration to effect followed by randomized withdrawal with a double-blind, placebo-controlled, parallel, multiple-dose design to evaluate chronic low back pain in opioid naïve patients (Study 031) and opioid experienced patients (Study 032) conducted at multiple centers in the U.S.

The two studies had similar findings. The efficacy was demonstrated by the primary outcome measure, the change in pain intensity from baseline to the final visit, and supported by the protocol-defined secondary outcome measures, time to discontinuation due to lack of efficacy, and patient and physician global evaluation of medication. Treatment differences based on additional analyses were also shown in the following measurements: the change in PI from baseline to the final visit adjusted for stabilized dose level, time-specific measure of average PI by visit, percent reduction in average PI, proportion of responders (≥30% reduction in PI), percent discontinued due to lack of efficacy, time to discontinuation and proportion discontinued due to all reasons, and the use of rescue medication over the first four days and the percent of days used during the remainder of the 12-week double-blind treatment period (no difference in Study 032 for the last outcome in the list).

The discontinuation from the open-label titration treatment was 37% due to all reasons and 26% due to AEs, lack of efficacy, and failure to meet titration-stabilization criteria in opioid naïve patients in Study 031, and 43% due to all reasons and 31% due to AEs, lack of efficacy, and failure to meet titration-stabilization criteria in opioid experienced patients in Study 032.

The stabilized dosage of oxymorphone ER was much higher in opioid-experienced patients than in opioid naïve patients and drug tolerance to the new opioid treatment was suggested by findings of worsening pain scores at the end of study in both trials.

Dose response in efficacy was suggested by observation of larger treatment differences in the higher dosage groups in both studies.

1.3.3 Safety

The length of exposure and the number of subjects exposed to long-term treatment appear adequate in the Overall database. The total exposure to oxymorphone ER treatment was reported in slightly over 2000 patients and to placebo treatment in more than 500 patients in all the Phase 2/3 ER trials, including the studies reported in the original submission. A total of 433 patients had at least six months of exposure and 267 of them had at least 12 months of exposure in the five open-label studies. The most frequent daily dose exposed was 10-50 mg/day (57%), followed by >90 mg/day (18%) and 50-90 mg/day (17%).

There were 14 new reports of deaths (13 cancer deaths and one non-cancer death) in addition to 35 deaths reviewed with the original submission. The causes of deaths were most likely attributable to complications associated with the disease progression of end-stage cancer (most cases had only 0.5-2.5 months of oxymorphone treatment) in 13 cancer deaths and to community-acquired pneumonia in one non-cancer death based on the review of narratives.

Serious AEs were reported in 150 (7.5%) of oxymorphone ER-treated subjects and the most common (0.5%) ones were chest pain, pneumonia, and vomiting in the Overall Safety database. The review of narratives of the six new cases of serious cardiac AEs identified in the Update Safety database did not appear to suggest cardiac toxicity associated with oxymorphone treatment.

The Overall dropout rate was more than 60% in oxymorphone-treated subjects. The dropouts were mainly due to AEs, especially, the AEs of CNS and GI systems commonly associated with the use of opioid drugs.

The most frequently occurring AEs in patients treated with oxymorphone ER were events expected in opioid users: nausea (35%), constipation (33%), dizziness (excluding vertigo, 19%), vomiting (17%), pruritus (17%), somnolence (17%), headache (12%), sweating increased (12%), and sedation (10%). The same set of symptoms was identified as the most common, treatment-related AEs.

Laboratory tests were not conducted in any of the new studies in the current submission. The review of laboratory findings suggested no safety signals for treatment-related decrease in WBC count and neutropenia (which were mostly due to laboratory sample mishandling) or LFT elevation.

Vital signs were recorded in the two controlled studies (031 and 032) in the current submission. Other than a trend of small decrease in systolic and diastolic blood pressure in the first few weeks of the open-label treatment in Study 031, there were no remarkable trends based on the changes in group mean values.

Based on the reanalysis of ECG data of the identified cases, QTc prolongation was mainly due to in treatment fluctuation because most of the QTc abnormalities were normalized upon rechallenge with the same or different oxymorphone formulations and the end-of-study measurements were normal in six of the seven cases. The ECG data from retrospective partial recollection of subjects treated in Studies 015, 020, and 025 provided no additional evidence for treatment-related QTc prolongation.

Eight cases of discontinuation due to opioid withdrawal symptoms were identified in Studies 031 and 032 although the group mean scores of COWS and ARS at each scheduled visit during the double-blind treatment did not show the signs of opiate withdrawal in the two treatment groups.

One case of on-study pregnancy was reported in Study 032 and ended as an elective abortion.

There were no new reports of overdose in the current submission.

There appeared to be an age-related increase in the incidence rates of dizziness and somnolence associated with oxymorphone treatment. The other observed higher incidence rates of some AEs in one subpopulation versus the other were probably due to normal variations.

1.3.4 Dosing Regimen and Administration

The efficacy and safety findings from the trials using titration-to-effect design support the proposed dosing regimen for opioid naïve patients. The proposed conversion from other opioids in the dosing instruction for opioid experienced patients is not supported by data because the studies of relative potency between oxymorphone ER and other opioids had not provided useful information about the relative potency.

1.3.5 Drug-Drug Interactions

There were no new studies of drug-drug interactions in the current submission.

1.3.6 Special Populations

Elderly patients have been shown to have increased risks to oxymorphone-induced respiratory/CNS depression at higher starting doses in a post-operative setting based on the results of studies in the original submission. There was also an age-related increase in incidence rates of dizziness and somnolence. Because elderly patients are at higher risk to oxymorphone-induced drug toxicity due to higher levels of

systemic exposure (about a 40% increase in total and maximum drug levels in comparison to younger subjects), oxymorphone treatment should be started at lower level with gradual titration under closer supervision.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established name of the product is oxymorphone hydrochloride (HCL) and the proposed name is OPANA™ ER. It is an extended-release formulation featured by the use of TIMERx®-N, a hydrophilic matrix as a controlled-release drug delivery excipient. Oxymorphone HCL is a semi-synthetic opioid-receptor agonist with the proposed mechanism of action at multiple CNS sites though interaction with opioid receptors.

The proposed indication is for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time, but not for mild pain, non persistent pain, or acute post-operative pain, or for use as a prn (as needed) analgesic.

The proposed adult dosage for opioid naïve patients is to initiate at 5 mg q12h followed by individualized titration at increments of 5-10 mg q12h every 3-7 days, to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician, and for opioid experienced patients, to convert from other opioids.

2.2 Currently Available Treatment for Indications

The currently available treatments for the indication are mainly opioid analgesics, combination products containing an opioid as an active ingredient, and tramadol.

2.3 Availability of Proposed Active Ingredient in the United States

The currently available drug products containing the active ingredient oxymorphone are Numorphan® injection 1 mg/ml and 1.5 mg/ml by subcutaneous and intramuscular administration (NDA 11-707) and Numorphan® oxymorphone rectal suppositories 5 mg (NDA 11-738).

2.4 Important Issues with Pharmacologically Related Products

As an opioid agonist oxymorphone has similar pharmacological effects as the other drugs of the same class as described in the product labeling for opioid drugs. The major safety issues with the use of opioids are their potential for misuse, drug abuse and addiction and the potential for respiratory depression, especially in the elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation. The interaction of the opioid products with alcohol and drugs of abuse and with other CNS depressants may cause respiratory depression, hypotension, profound sedation, or coma. A common problem associated with the chronic use of opioid is the development of drug dependence and tolerance.

2.5 Presubmission Regulatory Activity

The original submission of NDA 21-610 for oxymorphone ER dated December 19, 2002, was granted approvable by the Division on October 15, 2003. The Sponsor was requested to address a number of clinical deficiencies, which included providing replicable evidence for efficacy in a 12-week study of chronic pain and additional data to address safety concerns regarding liver function, WBC count, and QTC interval. In the subsequent interactions with the Sponsor as recorded in the meeting/teleconference minutes

dated October 31, 2003, March 16, 2004, and May 25, 2004 the need for additional evidence to support efficacy was re-emphasized, the Sponsor's explanations for laboratory abnormality were accepted, and QTC abnormality was still a safety concern requiring further investigation. On July 12, 2004, a new protocol (Study 031) was submitted under Special Protocol Assessment (SPA) for studying multiple-dose effects of oxymorphone ER in patients with chronic low back pain.

2.6 Other Relevant Background Information

There were ten phase 2/3 studies of oxymorphone ER submitted in the first review cycle, three multiple-dose efficacy studies, one single-dose efficacy study, three studies of relative potency with respect to other opioid, and three open-label extension safety studies (refer to the original review for detail).

The multiple-dose analgesic studies of osteoarthritis were placebo-controlled, parallel studies of 20 and 40 mg doses for four weeks (Study 015) and of 10, 40, and 50 mg doses for two weeks (Study 025). Statistically significant treatment differences in arthritic pain intensity (VAS) were not demonstrated in either study. The multiple-dose analgesic study of low back pain (Study 016) was designed in a similar way, but with shorter study duration in comparison to the two efficacy studies in the current submission. It had a design of titration-to-effect and randomized withdrawal with a placebo control and that the titration period was of no more than two weeks and was followed by an 18-day maintenance period, during which patients were given individualized dosing twice a day. Efficacy was supported by the results of the study. The single-dose analgesic study of the ER formulation (Study 012) raised the issues about safe use of the product in a post-operative setting. The three potency studies of a crossover design (Study 017, 018, and 019) did not result in providing useful information about the relative potency because of the design issues.

Another NDA for the drug product containing the same active ingredient in different formulation submitted originally at about the same time (December 20, 2002) was NDA 21-611 for oxymorphone immediate-release (IR) formulation. The two NDAs have been resubmitted on the same date. The efficacy and safety of oxymorphone IR will be reviewed separately.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Refer to the chemistry review.

3.2 Animal Pharmacology/Toxicology

Refer to the pharmacology/toxicology review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Efficacy data were from the two studies (Studies 031 and 032) of chronic low back pain. Safety data new to the current submission in the Update Safety database include data from the four newly completed studies: the two studies of chronic low back pain (Studies 031 and 032) and the two open-label studies of chronic pain (Studies 028 and 029), as well as the newly collected data from the two open-label extension

studies (Studies 021 and 022) already ongoing at the time of the 120-Day Safety data cutoff date. Overall safety data from all phase 2/3 studies are also used in the safety review.

4.2 Tables of Clinical Studies

Table 4-1 Summary of Newly Completed Clinical Studies Used as Data Sources

Protocol # # of sites	Study Type	Study Design	Dates of Study	Dosage	# of subj	Mean age/range (y) (range) Gender (M, F) Race (W, NW)	Data relevance
EN3202-031 31 sites	Dose ranging efficacy study in opioid-naïve patients with chronic low back pain	Open-label titration followed by randomized, double-blind, placebo-controlled	11/24/04-7/18/05	Titration to optimal doses of OM ER, and then OM ER or Placebo	325	50.1 (18-85) 160 M, 165 F 289 W, 36 NW	Efficacy and safety
EN3202-032 30 sites	Dose ranging efficacy study in patients with chronic low back pain	Open-label titration followed by randomized withdrawal, double-blind, placebo-controlled	10/13/04-8/19/05	Titration to optimal doses OM ER ≥20mg, and then OM ER or Placebo	250	49.1 (21-85) 118 M, 132 F 219 W, 31 NW	Efficacy and safety
EN3202-028 29 sites	Safety study in opioid-naïve patients with chronic (non malignant) pain	Multi-center, open-label	6/11/03-1/21/04	OM ER 5mg tab OM ER 10mg tab OM ER 20mg tab	126	56.2 (19-84) 55 M, 71 F 112 W, 14 NW	Safety
EN3202-029 40 sites	Safety study in patients with cancer or neuropathic pain	Multi-center, open-label	8/22/03-3/5/05	OM ER 5mg tab OM ER 10mg tab OM ER 20mg tab OM ER 40mg tab	221	56.8 (19-85) 123 F, 98 M 202 W, 19 NW	Safety
EN3202-021 44 sites	Safety study in adults with cancer pain or chronic lower back pain	Multi-center, open-label	3/14/01-7/2/03	Completed studies 016 & 019; Dose titration in the first week	239	48.0 (24-81) 128 M, 111 F 221 W, 18 NW	Safety
EN3202-022 25 sites	Safety study in cancer patients with moderate to severe pain	Multi-center, open-label	4/19/01-12/31/02	Completed study 018; Starting dosage from previous controlled-study; Dose titration	24	57.0 (36-71) 19 F, 5 M 21 W, 3 NW	Safety

Source: Supplemental Table 1 on pages 61 to 69 of the updated safety report.

4.3 Review Strategy

Each efficacy study is reviewed in detail in Section 10 and the results of the two efficacy studies are discussed together in Section 6. Review of safety is based on the pooled safety data from all phase 2/3 studies grouped into three categories: the Updated Safety database consisted of data from the six studies with new data in the current submission, the 120-Day Safety database consisted of safety data already reviewed in the first review cycle, and the Overall Safety database combining the two.

4.4 Data Quality and Integrity

Two clinical sites, Site 13 (with enrollment of seven patients in Study 031 and 38 patients in Study 032) and Site 29 (with enrollment of 32 patients in Study 031 and 15 patients in Study 032), were selected for inspection. Inspection of site 13 (Investigator: Martin Hale, M.D.) revealed under reporting of VAS scores at five occasions in three subjects in the oxymorphone ER treatment groups as summarized in the table below.

Table 4-2 Data Discrepancy at Site 13 of Study 032

Subject	Visit #	Duration of double-blind treatment	VAS reported by subject as shown in source document	VAS reported by subject as listed in CRF
2009	10	4 weeks	18 mm	12 mm
2011	14	12 weeks	67 mm	57 mm
2034	8	2 weeks	15 mm	9 mm
2034	9	3 weeks	15 mm	9 mm
2034	14	12 weeks	15 mm	10 mm

Two of these under reported scores for the 12-week assessment were included in the dataset for the primary analyses

Inspection of Site 29 (Investigator: Gilbert Podolsky, M.D.) revealed only one case of dosing error where the subject was randomized to 25 mg, instead of the correct dose of 30 mg, and received the dose for several days before the error was discovered.

4.5 Compliance with Good Clinical Practices

The steps to ensure the accuracy and reliability of data included the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigators and associated personnel prior to the start of the study, and periodic monitoring visits by Sponsor personnel. Sponsor personnel reviewed CRFs for accuracy and completeness before, during, and after on-site monitoring visits; any discrepancies were resolved with the Investigator or designee, as appropriate. CRF data were entered into a clinical database by the electronic data capture system. After the resolution of data queries, the database was locked and the data transferred to the statistician.

Selective audits of five sites, Sites 12, 23, 29, 31, and 35, with a total enrollment of 106 patients in Study 031 and 62 patients in Study 032, were performed by Endo Pharmaceuticals Inc. to evaluate compliance with Good Clinical Practice guidelines according to the requirements of Endo's Quality Assurance Audit Plan. The Sponsor provided the audit certificate in the submission.

4.6 Financial Disclosures

The financial disclosure form signed by the Sponsor certified that no financial arrangements had been made, where outcomes affects compensation, with any Principle Investigator or sub-investigators involved in the clinical studies, and that these Investigators had no proprietary, significant equity interest, or any significant payments of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Refer to clinical pharmacology review.

5.2 Pharmacodynamics

Refer to the clinical pharmacology review.

5.3 Exposure-Response Relationships

Refer to the clinical pharmacology review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for the oxymorphone extended-release formulation is for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time (not intended for use as a prn analgesic).

6.2 Methods

There are two controlled efficacy studies EN3202-031 and EN3202-032 with similar designs. The results of each of these two studies are reviewed in detail in Section 10. The efficacy findings from both studies are discussed together in this section as evidence to support efficacy claim.

6.3 General Discussion of Endpoints

The efficacy endpoints are listed below:
Primary efficacy endpoint:
Change in average pain intensity (VAS) (of past 24 hours) from baseline to final visit

Secondary efficacy endpoints:
- Change from baseline to final visit in patient's global assessment of pain medication
- Change from baseline to final visit in physician's global assessment of pain medication
- Change from baseline to final visit in Pain Quality Assessment Scale (Study 032 only)
- Evaluation of compliance and study medication usage, time to discontinuation due to lack of efficacy

Additional efficacy endpoints (in study report and not predefined in the protocol) were:
- Average PI by visit
- Change in average PI from baseline to final visit adding stabilized dose level as a factor
- Percent reduction in average PI
- Proportion of responders as defined by ≥30% reduction in PI
- Time to discontinuation due to all reasons
- Proportion discontinued due to all reasons
- Average daily dose of rescue medication during the first four days of double-blind treatment

• Days on rescue medication from Day 4 to final visit

In the efficacy studies of chronic pain indications the most commonly used primary efficacy endpoint is the change of pain intensity from baseline to final clinic visit. The efficacy endpoints of secondary importance in chronic analgesic studies are functional assessment and patient global evaluation. However, the functional assessment was neither in the study plan nor in any previous communications with the Sponsor. The assessment of the use of rescue medication is also considered important in the efficacy evaluation of analgesics for chronic pain indications. The choices of the primary and secondary efficacy endpoints were agreed between the Division and the Sponsor through Special Protocol Assessments and meetings. In this reviewer's opinion, the addition of functional assessment of chronic analgesic effects of the study drug would make the set of endpoints more adequate in providing reasonable assessment of clinical benefit.

6.4 Study Design

The two studies (031 and 032) had a very similar design. They were studies of open-label, titration to effect followed by randomized withdrawal with a double-blind, placebo-controlled, parallel, multiple-dose design to evaluate chronic low back pain in opioid naïve patients (Study 031) and opioid experienced patients (Study 032) conducted at multiple centers in the U.S.

The findings from the three chronic pain studies in the original submission have suggested a withdrawal design of having a better chance of demonstrating efficacy than a straight parallel design. The withdrawal design using an enriched population is one approach to address the problem with missing data due to high dropout rates commonly encountered in a study of a straight parallel design. It deals with the problem upfront by eliminating the non-responders before randomization instead of waiting for them to dropout during the study. However, the interpretation of the results of a randomized withdrawal study should take the following factors into consideration. The study by design may overestimate benefit by showing greater treatment differences in responders than what would be expected from a more general study population and underestimate toxicity by excluding those who can not tolerate the drug and thus have fewer reports of adverse events. The proportion of non-responders who dropped out during the open-label titration period should be counted in the report of outcome.

There were no **active controls** included in the studies and thus, no intention to assess the **relative potency** to other approved modified-release opioid analgesics. Having an active control in a setting of individualized dosing might not provide accurate information on relative potency anyway in this reviewer's opinion.

In both studies patients on the placebo arm had sudden switch from opioid treatment to placebo, which could potentially lead to opioid withdrawal symptoms and make the maintenance of **blinding** difficult. The effort in minimizing the **potential bias** was by allowing rescue medication, oxymorphone IR 5 mg q4-6h in the first four days. The dose restriction of rescue to $\leq$2 doses/day after the first four days would help to reduce **confounding** effect of rescue.

The choice of the **study population**, patients with chronic non-neuropathic low back pain who were opioid naïve (Study 031) and opioid experienced (Study 032), was consistent to the proposed indication and considered representative samples of the target population. Chronic low back pain has been increasingly used as a reliable model in evaluation of chronic pain. The studies of oxymorphone in both opioid naïve and opioid experienced patients could provide useful information on how to use the drug in these different populations and about whether there is a differential response to the study drug with respect to the past opioid experience.

The choice of individualized **dosing regimen** was based on the information obtained from previous controlled trials on fixed dose levels (Studies 015 and 025) individualized dosing regimen (Study 016) in the original submission (refer to the related reviews for detail), and preceding open-label studies of upward titration (Studies 028 and 029) in the current submission. The data obtained from the studies of individualize dosage provided essential information in formulating the dosing recommendation in the proposed labeling.

The 12-week double-blind **treatment duration** is commonly required length of time to study durability effect of chronic analgesics. Controlled trials of longer duration (>12 weeks) might be able to provide more information on long-term efficacy since the development of drug tolerance is a potential problem with chronic use of opioids.

6.5 Efficacy Findings

The results of the treatment comparison between oxymorphone ER and placebo are summarized for the two studies in the table below. The treatment differences between the oxymorphone ER treatment group and placebo were highly statistically significant for the primary efficacy endpoint and all the secondary and additional endpoints tested.

The effect size of the treatment difference was remarkable in almost all efficacy endpoints studied.

- The mean increase in pain intensity from baseline to final visit (**primary endpoint**) in the oxymorphone ER group was much smaller than the placebo group (an increase of 11 mm with oxymorphone ER treatment versus 28 mm with placebo treatment in Study 031 and 9 mm versus 32 mm in Study 032).

- The proportion of patients discontinued due to lack of efficacy in the oxymorphone ER group was much smaller than the placebo group (10% in the oxymorphone ER group versus 36% in the placebo group in Study 031 and 12% versus 54% in Study 032).

- The proportion of patients discontinued due to all reasons in the oxymorphone ER group was also much smaller than the placebo group (33% in the oxymorphone ER group versus 55% in the placebo group in Study 031 and 29% versus 74% in Study 032).

- The proportion of patients who assessed their pain medication as good, very good, or excellent at the final visit was much higher in the oxymorphone ER group than placebo group (82% in the oxymorphone ER group versus 40% in the placebo group in Study 031 and 80% versus 33% in Study 032).

- Physician's global evaluation of medication showed the same pattern that the proportion of evaluation as good, very good, or excellent for patients on oxymorphone ER was much higher than for patients on placebo (83% in the oxymorphone ER group versus 37% in the placebo group in Study 031 and 85% versus 28% in Study 032).

- The change in the total Pain Quality Assessment scores (PQAS-20) from baseline to final visit was much smaller in patients on oxymorphone ER than on placebo (5.5 in the oxymorphone ER group versus 40.5 in the placebo group in Study 032; the parameter was not studied in Study 031).

- The incorporation of patients' stabilized dose levels in the statistical model of the primary analyses did not change the magnitude of the treatment difference between the two study arms in either study.

- The percentage of responders defined by a ≥30% reduction in average pain intensity from screening to the final visit was much higher in the oxymorphone ER group than the placebo group (81% in the oxymorphone ER group versus 52% in the placebo group in Study 031 and 80% versus 35% in Study 032).

- The increase in the amount of daily rescue usage from Day 1 to Day 4 (with no dose restriction in the first four days) of the double-blind treatment was smaller in the oxymorphone ER group than the placebo group (up to 3.3 mg/day in the oxymorphone ER group versus 10.3 mg/day in the placebo group in Study 031 and up to 6.5 mg/day versus 15.6 mg/day in Study 032).

- The percentage of days over which the rescue was used during the time interval from Day 5 until the end of the double-blind treatment (rescue restricted to two doses/day) was smaller in the oxymorphone ER group than the placebo group (34 to 42% in the oxymorphone ER group versus 55 to 65% in the placebo group) in Study 031 and was similar for the 2 treatment arms in Study 032.

- The durability of treatment effects over the entire 12-week double-blind treatment period and associated effect size of treatment differences could also be appreciated visually in the graphs of the pain curves of visit-specific average pain intensity, as well as the survival curves for the time to discontinuation due to lack of efficacy and due to all reasons (refer to the review of individual studies).

Table 6-1 Summary of the Efficacy Results of Study 031 and Study 032

	Study 031			Study 032		
Statistics	Oxymorphone ER (N=97)	Placebo (N=95)	p-value	Oxymorphone ER (N=69)	Placebo (N=69)	p-value
Primary endpoint						
Baseline pain intensity (VAS) mean (STD)	**18.5** (11.22)	**19.3** (11.26)	--	**23.9** (12.05)	**22.2** (10.75)	--
Final visit PI (VAS) mean (STD)	**29.9** (26.21)	**46.2** (27.03)	--	**31.3** (23.48)	**54.5** (28.43)	--
Change in PI, LSMean±SE	**10.6 ± 2.50**	**27.7 ± 2.53**	<0.0001	**8.7 ± 2.95**	**31.6 ± 2.93**	<0.0001
Secondary endpoints						
Time to discontinuation due to lack of efficacy			<0.0001			<0.0001
Number (%) discontinued due to lack of efficacy	10/97 (10.3%)	34/95 (35.8%)		8/69, (11.6%)	37/69 (53.6%)	
Patient global at final visit Proportion with ≥good evaluation	78/95 (82.2%)	34/86 (39.5%)	<0.0001	55/69 (79.7%)	22/67 (32.8%)	<0.0001
Physician global at final visit Proportion with ≥good evaluation	80/96 (83.4%)	32/87 (36.7%)	<0.0001	58/69 (84.5%)	18/65 (27.7%)	<0.0001
Change in PQAS-20, LSMean				5.5	40.5	<0.0001
Additional endpoints						
Change in PI with respect to dose level, LSMean	10.6	27.7	<0.0001	8.6	31.6	<0.0001
Responders: ≥30% PI decrease	79/97 (81.4%)	47/91 (51.7%)	<0.0001	55/69 (79.7%)	23/66 (34.8%)	<0.0001
Time to discontinuation due to all reasons			<0.0007			<0.0001
Proportion discontinued due to all reasons	32/97 (33.0%)	52/95 (54.7%)		20/69 (29.0%)	51/69 (73.9%)	
Daily rescue in first 4 days of double-blind treatment	↑ from 2.2 mg to 3.3 mg	↑ from 2.3 mg to 10.3 mg		↑ from 5.6 mg to 6.5 mg	↑ from 11.0 mg to 15.6 mg	
% of days on rescue medication: Day 4 to final visit	34.4 - 41.2%	55.1 - 65.3%		61.8-70.7%	62.2-66.7%	

The discontinuation from the open-label titration treatment was 37% due to all reasons and 26% due to AEs, lack of efficacy, and failure to meet titration-stabilization criteria in opioid naïve patients in Study

031, and 43% due to all reasons and 31% due to AEs, lack of efficacy, and failure to meet titration-stabilization criteria in opioid experienced patients in Study 032.

In terms of other factors that might have potential impact on the study results, the treatment groups in the two studies were basically balanced with regard to the demographic characteristics such as age, gender, race, and weight and with regard to the etiology of low back pain and the baseline pain intensity. There were no statistically significant interactions between the average pain intensity and demographic and screening disease characteristics.

The distribution of individual dosing levels at randomization was similar between the two treatment groups in opioid naïve patients in Study 031 and had more variations in opioid experienced patients in Study 032. The mean daily dose at stabilization was doubled in opioid experience patients (about 80 mg/day) in comparison to opioid naïve patients (about 40 mg/day).

There were differential dropout rates of about 30% in the oxymorphone ER treatment group (in both studies), and 53% (study 031) to 74% (study 032) in the placebo group, where most dropouts in the placebo group were due to lack of efficacy as expected.

The methods used in imputation of missing values were considered acceptable. However, the methods used in the sensitivity analyses were much less conservative than what was used in the original plan. The results of the two sensitivity analyses were consistent with that of the primary analyses.

About 30% patients who received double-blind treatment had protocol deviations occurred at some point during the entire study (both open-label phase and double-blind phase), mostly due to off-schedule visit and missing visit. More cases of protocol deviation were reported in patients in the oxymorphone ER group than the placebo group. The types of protocol deviation were not considered as having a noticeable impact on the results of primary and secondary efficacy evaluations. The potential impact could only have been on the change in PI by visit (one of the additional efficacy parameters). The impact of off-schedule visit and missing visit had limited effect because of the relatively long time interval (one to two weeks) between the scheduled clinic visits (unlike hourly assessments) and the imputation rules for missing data specified in the data analysis plan.

In Study 031 a modified intention-to-treat (MITT) population was used for efficacy analyses. The MITT population excluded 13 patients (eight on oxymorphone ER and five on placebo), who were on oxymorphone ER 10 mg/day (5 mg BID) at the study entry, for failing to stabilize on a minimum of 20 mg total daily dose. The results of analyses based on the entire ITT population were consistent to the results obtained from MITT-based analyses. In Study 032 the Sponsor excluded four patients (one on oxymorphone and three on placebo) from the ITT efficacy analyses because they did not sign the HIPAA consent form to have their data eligible for efficacy analysis. The exclusion of this magnitude was considered unlikely to change study results and efficacy conclusion if data would have been reanalyzed. . The possible explanations for the worsening of pain from baseline to the final visit while on oxymorphone treatment are tolerance to the opioid treatment in opioid naïve patients and tolerance to the new type of opioid treatment in opioid experienced patients.

The results of subgroup analyses revealed a larger treatment difference in the subgroup stabilized at a higher daily dose than at a lower daily dose in both studies, suggesting possibly a dose response in efficacy. Gender difference was opposite in the two studies and thus non conclusive. Because of the relatively small sample size for the groups of elderly, non-Caucasian, and patients with severe pain at the screening, the treatment differences with respect to these variables could not be adequately evaluated.

6.6 Clinical Microbiology

Not applicable.

6.7 Efficacy Conclusions

Oxymorphone ER studied at individualized dosage in highly selected responders was shown to be efficacious in treating chronic low back pain based on the replicable positive findings from the two studies.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

A total of 49 deaths had been reported from all clinical trials in the oxymorphone development program. In addition to the 35 cases of deaths (34 cancer death and one non-cancer death) discussed in the safety review of the original submission, there were 14 cases of deaths reported in patients on oxymorphone treatment in the current submission. Thirteen of the 14 cases in the open-label safety studies (one case in Study 021, one case in Study 028, and 11 cases in Study 029) were cancer deaths most likely attributable to complications associated with the disease progression of end-stage cancer (most cases had only 0.5-2.5 months of oxymorphone treatment preceding deaths) based on the review of narratives. One death was reported from the study of low back pain (Study 032). The cause of death was unlikely to be related to the study drug based on the review of the narrative below.

Patient 001-016 was a 73-year-old Caucasian female with chronic low back pain. Her medical history was notable for hypertension, Type II diabetes, diabetic neuropathy, hyperlipidemia, Parkinson's disease, acid reflux, cervical spondylosis, osteoarthritis, left shoulder and arm pain, myofascial pain, three myocardial infarctions (1991, 1993, 1995), quadruple bypass surgery (1995), stent placement ([redacted]), mastectomy due to breast cancer, cholecystectomy, and cervical and lumbar laminectomy. She was treated with OxyContin 10 mg po tid and oxycodone 5 mg po qid from 2003 to April 3, 2005 for chronic low back pain. Her other concomitant medications included Neurontin, metoprolol, Lasix, Plavix, aspirin, Lantus insulin, Humalog, primidone, Aciphex, Phenergan, and Zyrtec. On April 4, 2005, she was enrolled in the study open-label titration period and began taking oxymorphone ER 10 mg po q12h and oxymorphone IR 5 mg PO prn (limited to 2 doses per day for breakthrough pain). Prior to enrollment in the study, the patient developed a sinus infection on April 1, 2005. She was admitted to the hospital on . [redacted] and was treated for pneumonia. She stopped taking the study drug on the morning of April 5, 2005. The patient re-started the study drug on April 14, 2005. She was seen by her physician on [redacted] and she was again admitted to the hospital in the evening for pneumonia. The patient was administered cefepime 1000 mg IV q24h from April 16 – 24, 2005. Oxymorphone IR was discontinued on April 21, 2005 and Oxymorphone ER was discontinued on April 23, 2005 due to missing study visits. The study investigator gave verbal orders to the attending physician to start the patient on OxyContin 10 mg tid and oxycodone 5 mg po qid for pain control. The patient was given OxyContin 10 mg PO QD on April 25 and April 26, 2005. The investigator assessed the event as unlikely related to the study drug but rather to a community-acquired infection.

7.1.2 Other Serious Adverse Events

In the Overall database 150 (7.5%) of oxymorphone ER-treated subjects and 11 (2.1%) of placebo subjects experienced one or more SAE during their participation in the studies. Incidence rates for the oxymorphone ER treatment-emergent, non-fatal SAEs are presented by preferred term in the table below, which includes only the more frequently occurring SAEs reported in **at least three subjects in the Overall database or at least two subjects in the Update database** (safety data submitted only in the current submission). The most frequently occurring (0.5%) individual SAEs were chest pain (11 subjects), pneumonia (11 subjects), and vomiting (10 subjects). There were several SAEs reported by more subjects in the Update database in this submission than subjects in the 120-Day Safety database (safety data submitted during the first review cycle), including pneumonia in eight subjects, confusional state in four subjects, cholelithiasis, malignant pleural effusion, pain, chest pain aggravated, drug withdrawal syndrome, hypoxia, intractable pain, malignant neoplasm progression, mental status changes, obstructive uropathy, renal failure, and respiratory failure, each in two subjects.

Table 7-1 Number (%) of Oxymorphone ER-treated Patients with Non-Fatal SAEs in Descending Frequency in Phase 2/3 ER Trials

	120-Day Safety	Update	Overall
Total # patients treated with oxymorphone ER	(N = 1089)	(N = 972) [a]	(N = 2011) [b]
MedDRA preferred term			
Any adverse events	93 (8.5)	62(6.4)	150 (7.5)
Chest pain NEC	7 (0.6)	4 (0.4)	11 (0.5)
Pneumonia NOS	3 (0.3)	8 (0.8)	11 (0.5)
Vomiting NOS	8 (0.7)	3 (0.3)	10 (0.5)
Dehydration	5 (0.5)	4 (0.4)	9 (0.4)
Nausea	6 (0.6)	4 (0.4)	9 (0.4)
Dyspnoea NOS	5 (0.5)	1 (0.1)	6 (0.3)
Abdominal pain NOS	4 (0.4)	2 (0.2)	5 (0.2)
Back pain	3 (0.3)	1 (0.1)	4 (0.2)
Confusional state	0 (0.0)	4 (0.4)	4 (0.2)
Drug interaction NOS	4 (0.4)	0 (0.0)	4 (0.2)
Hypotension NOS	3 (0.3)	1 (0.1)	4 (0.2)
Osteoarthritis aggravated	4 (0.4)	0 (0-0)	4 (0.2)
Pulmonary embolism	2 (0.2)	2 (0.2)	4 (0.2)
Pyrexia	2 (0.2)	2 (0.2)	4 (0.2)
Urinary retention	3 (0.3)	1 (0.1)	4 (0.2)
Atrial fibrillation	3 (0.3)	0 (0.0)	3 (0.1)
Cholelithiasis	1 (0.1)	2 (0.2)	3 (0.1)
Chronic obstructive airways disease exacerbated	2 (0.2)	1 (0.1)	3 (0.1)
Concomitant disease progression	2 (0.2)	1 (0.1)	3 (0.1)
Depressed level of consciousness	3 (0.3)	0 (0.0)	3 (0.1)
Malignant pleural effusion	1 (0.1)	2 (0.2)	3 (0.1)
Pain exacerbated	2 0.2)	1 (0.1)	3 (0.1)
Pain in limb	3 (0.3)	0 (0.0)	3 (0.1)
Pain NOS	1 (0.1)	2 (0.2)	3 (0.1)
Urinary tract infection NOS	3 (0.3)	0 (0.0)	3 (0.1)
Venous thrombosis deep limb	3 (0.3)	0 (0.0)	3 (0.1)
Chest pain aggravated	0 (0.0)	2 (0.2)	2 (0.1)
Drug withdrawal syndrome	0 (0.0)	2 (0.2)	2 (0.1)
Hypoxia	0 (0.0)	2 (0.2)	2 (0.1)
Intractable pain	0 (0.0)	2 (0.2)	2 (0.1)
Malignant neoplasm progression	0 (0.0)	2 (0.2)	2 (0.1)
Mental status changes	0 (0.0)	2 (0.2)	2 (0.1)
Obstructive uropathy	0 (0.0)	2 (0.2)	2 (0.1)
Renal failure NOS	0 (0.0)	2 (0.2)	2 (0.1)
Respiratory failure	0 (0.0)	2 (0.2)	2 (0.1)
Syncope	0 (0.0)	2 (0.2)	2 (0.1)

[a] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
[b] Overall column includes all serious AEs, some of which may not be classified as serious before the 120-Day Safety cutoff date but later became serious.
Source: Table 16 on pages 171-179.

Serious cardiac AEs are selected to be reviewed in detail because of the safety issues regarding to the questionable QTc prolongation discussed in the original NDA review. As shown in the table below, six cases of serious cardiac AEs were identified in the Update safety database (one placebo patient in Study 031 and five patients treated with oxymorphone: one in Study 032 and four in Study 029). All six cases resolved with no sequela and were considered unlikely to be related to the study drug in the Investigators' opinion. Three of the six cases had continuous treatment while the AEs occurred, one had an interruption in treatment, and two were discontinued from the treatment due to the AEs. These events did not suggest a

causal relationship by the study drug based on the review of narratives. As shown in the three examples provided below the events were more likely attributable to the concurrent medical conditions such as a positive medical history of cardiovascular disease.

Table 7-2 Number (%) of Oxymorphone ER-treated Patients with Non-Fatal *Cardiac* Serious AEs in Phase 2/3 ER Trials

	120-Day Safety	Update	Overall
Total # patients treated with oxymorphone ER	(N = 1089)	(N = 972)	(N = 2011)
MedDRA preferred term			
Arrhythmia NOS	1 (0.1)	0 (0.0)	1 (0.0)
Atrial fibrillation	3 (0.3)	1 (0.1)	4 (0.2)
Atrial flutter	0 (0.0)	1 (0.1)	1 (0.0)
Cardiac failure congestive	1 (0.1)	1 (0.1)	2 (0.1)
Cardio-respiratory arrest	1 (0.1)	0 (0.0)	1 (0.0)
Coronary artery occlusion	1 (0.1)	0 (0.0)	1 (0.0)
Myocardial infarction	2 (0.2)	0 (0.0)	2 (0.1)
Oedema lower limb	1 (0.1)	0 (0.0)	1 (0.0)
Sinus tachycardia	0 (0.0)	1 (0.1)	1 (0.0)
Supraventricular tachycardia	1 (0.1)	0 (0.0)	1 (0.0)
Tachycardia NOS	0 (0.0)	1 (0.1)	1 (0.0)
Ventricular tachycardia	0 (0.0)	1 (0.1)	1 (0.0)

Source: Table 16 on pages 171-179.

Sample cases of serious cardiac AEs are described below.

Atrial fibrillation--Subject EN3202-031-017-1006 was a 58-year-old male who received placebo during the study and experienced atrial fibrillation. He had a significant cardiac history for coronary artery disease, prior MI, hypertension, atrial fibrillation, and by-pass surgery.

Atrial flutter--Subject EN3202-029-212-010 was an 83-year-old male who received oxymorphone ER 20 mg-40 mg/day for cancer pain from 1/29/04 until 8/5/04. The subject had a history of hypertension, coronary artery disease, and myocardial infarction. Concomitant medications included simvastatin, lisinopril, Aranesp, carboplatin and taxotere. The subject experienced pneumonia and atrial flutter on [redacted] and was treated with IV diltiazem and amiodarone. He continued with study drug after the event without further episodes of atrial flutter. In the opinion of the investigator, the event of atrial flutter was related to subject's pre-existing cardiac disease. The subject had progression of disease and was discharged from the study.

Ventricular tachycardia--Subject EN3202-029-206-003 was an 82-year-old male who received oxymorphone ER 5 mg BID along with oxymorphone IR 5 mg PRN for cancer pain from 1/21/04 until 6/28/04. The subject's medical history included prostate cancer, myocardial infarction and hypertension. The subject experienced ventricular tachycardia and rectal hemorrhage on [redacted] An ECG showed two types of ventricular tachycardia with different morphologies one of which may be an example of a different circuit with some variation occurring spontaneously. It was doubted that it was supraventricular with aberrant conduction. In the opinion of the investigator, the events were unlikely to be related to study medication but more likely to be a consequence of the subject's previous myocardial infarction and depressed ventricular systolic function. The subject continued with study drug post adverse events until 6/28/04 with no further episodes of the event.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The disposition of subjects by treatment groups during the Phase 2/3 oxymorphone ER clinical trials is summarized in the table below. In the **Overall database**, 1828 subjects received oxymorphone ER and 522 subjects received placebo. The oxymorphone-treated subjects include 807 subjects from all the open-label studies of the entire database, 347 of whom were subjects from the open-label Studies 028 and 029 in the current submission. **Discontinuation** occurred in 64% subjects treated with oxymorphone ER and 45% of subjects treated with placebo (note: not all trials had a placebo arm). The most frequently reported reasons for discontinuation were AEs (35%) for the oxymorphone ER treatment group and lack of efficacy (32%) for the placebo group. The pattern of early discontinuation was similar between the **Update database** and the original 120-Day Safety database. The total rate of discontinuation was similar for the oxymorphone ER and placebo treatment groups in the Update database.

Only five of the 14 deaths in Update database were counted as the cause of discontinuation because most other cases had major events preceding death being listed as the reasons for dropouts.

Table 7-3 Disposition of All Subjects by Treatment Groups in Phase 2/3 Oxymorphone ER Trials

	Oxymorphone ER			Placebo		
Patient Status [a]	120-Day Safety	Update	Overall	120-Day Safety	Update	Overall
Treated	1078 (100.0)	750 (100.0)	1828 (100.0)	350 (100.0)	172 (100.0)	522 (100.0)
Complete	407 (37.8)	240 (32.0)	667 (36.5)	221 (63.1)	65 (37.8)	286 (54.8)
Ongoing [b]	25 (2.3)	0 (0.0)	0 (0.0)			
Discontinued	646 (59.9)	510 (**68.0**)	1161 (**63.5**)	129 (36.9)	107 (**62.2**)	236 (**45.2**)
Adverse events [c]	394 (36.5)	242 (32.3)	639 (**35.0**)	20 (5.7)	16 (9.3)	36 (6.9)
Death	0 (0.0)	5 (0.7)	5 (0.3)			
Lack of efficacy	84 (7.8)	51 (6.8)	135 (7.4)	94 (26.9)	74 (43.0)	168 (**32.2**)
Lost to follow-up	18 (1.7)	23 (3.1)	42 (2.3)	4 (1.1)	2 (1.2)	6 (1.1)
Other	150 (13.9)	189 (25.2)	340 (18.6)	11 (3.1)	15 (8.7)	26 (5.0)

[a] Patients are categorized according to the last treatment received in the last trial in which they participated.
[b] The Ongoing patients at 120-day Safety Update either completed or discontinued study at this safety update.
[c] This category includes patients who discontinued the study due to Adverse Event reported on either the Study Termination or Adverse Event or Opioid Symptom Checklist CRF page. Patient EN3202-029-212-012 was considered as discontinued Due to AE, although the Study Termination Reason was listed as Investigator Opinion.
Source: Tables 1 and 2 on pages 16 and 17.

7.1.3.2 Adverse events associated with dropouts

Adverse events associated with dropouts of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER trials are presented by preferred term in the table below, which includes only the more frequently occurring AE-related discontinuation in at least 10 (0.5%) subjects. In the **Overall database** 32% of oxymorphone ER-treated subjects discontinued due to an AE. The most frequent AE-related discontinuation was due to AEs of CNS and GI systems and general AEs. AEs resulting in the discontinuation of 1% or more of oxymorphone ER-treated subjects included nausea (10.7%), dizziness (excluding vertigo, 6.2%), vomiting (5.4%), somnolence (3.6%), constipation (3.5%), pruritus (2.8), headache (2.1), sweating increased (1.8), sedation (1.6), and fatigue (1.4). The incidence rates for AEs leading to discontinuation were lower in the **Update safety database** than in the original 120-Day Safety database for the total AEs as well as the individual AEs.

[*Reviewer's comments: A possible explanation for the lower rate of discontinuation due to AEs in the Update database than the original 120-Day database is that all the subjects in the newly completed chronic*

studies underwent dose titration to a level of individually tolerated dose.]

Table 7-4 Number (%) of Oxymorphone ER-treated Patients with AEs Causing Dropouts in Descending Frequency in Phase 2/3 ER trials

	120-Day Safety	Update	Overall
Total # patients treated with oxymorphone ER	(N = 1089)	(N = 972) [a]	(N = 2011) [b]
MedDRA preferred term			
Any adverse events	391 (35.9)	251 (25.8)	642 (31.9)
Nausea	157 (14.4)	59 (6.1)	216 (10.7)
Dizziness (exc vertigo)	93 (8.5)	32 (3.3)	124 (6.2)
Vomiting NOS	85 (7.8)	23 (2.4)	108 (5.4)
Somnolence	43 (3.9)	29 (3.0)	72 (3.6)
Constipation	45 (4.1)	26 (2.7)	71 (3.5)
Pruritus NOS	39 (3.6)	18 (1.9)	57 (2.8)
Headache NOS	26 (2.4)	16 (1.6)	42 (2.1)
Sweating increased	27 (2.5)	10 (1.0)	37 (1.8)
Sedation	26 (2.4)	6 (0.6)	32 (1.6)
Fatigue	16 (1.5)	12 (1.2)	28 (1.4)
Insomnia NOS	10 (0.9)	9 (0.9)	19 (0.9)
Abdominal pain NOS	10 (0.9)	8 (0.8)	18 (0 .9)
Diarrhoea NOS	11 (1.0)	6 (0.6)	17 (0.8)
Dry mouth	13 (1.2)	4 (0.4)	17 (0.8)
Lethargy	8 (0.7)	8 (0.8)	16 (0.8)
Concomitant disease progression	(0.8)	2 (0.2)	14 (0.7)
Confusion	(1.2)	0 (0.0)	14 (0.7)
Anxiety NEC	6 (0.6)	6 (0.6)	12 (0.6)
Dyspnoea NOS	6 (0.6)	5 (0.5)	11 (0.5)
Nervousness	5 (0.5)	6 (0.6)	11 (0.5)
Appetite decreased NOS	7 (0.6)	3 (0.3)	10 (0.5)
Disorientation	7 (0.6)	3 (0.3)	10 (0.5)

[a] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
[b] Overall column includes all AEs causing study drug discontinuation, some of which may not be included in the other two columns since these AEs existed before the 120-Day Safety Update, but the subject later discontinued without the AE worsening in severity.
Source: Table 18 on pages 184 to 196.

7.1.3.3 Other significant adverse events

Refer to the original NDA safety review.

7.1.4 Other Search Strategies

None.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the four new chronic studies (028, 029, 031, and 032) adverse events were monitored and recorded throughout the trials. Safety data were collected at scheduled weekly visit during the titration period (all studies) and at monthly visit during the maintenance period in Studies 028 and 029 and at Day 4 and Weeks 1, 2, 3, 4, 6, 8, 10, and 12 during the double-blind treatment in Studies 031 and 032. In Studies 031

and 032 vital signs were recorded during most of the clinic visits (screening and weekly visit for the open-label phase; baseline and visits at Day 4, Weeks 1, 2, 3, 4, 8, and 12 for the double-blind phase) and withdrawal symptoms were assessed by using the Adjective Rating Scale for Withdrawal (ARS) and the Clinical Opiate Withdrawal Scale (COWS) at screening, baseline, and visits during the first four weeks of double-blind treatment. Any AE that was ongoing at completion/termination of the study was followed until resolution or up to 30 days.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The coding of AEs using preferred terms and categorization of AEs into system organ class by MedDRA were appropriate.

7.1.5.3 Incidence of common adverse events

In the **Overall database** AEs were reported in 1702 (85%) of oxymorphone ER-treated subjects and 296 (57%) of placebo subjects in the oxymorphone ER Phase 2/3 studies. The incidence of the most common AEs occurring in ≥5% subjects in all the Phase 2/3 studies (with or without the control groups) are presented by preferred term (in descending frequency in the Overall database) in the table below. The most frequently occurring treatment-emergent AEs in patients treated with oxymorphone ER were nausea (35.4%), constipation (33.3%), dizziness (excluding vertigo, 19.3%), vomiting (17.2%), pruritus (16.9%), somnolence (16.6%), headache (11.6%), sweating increased (11.5%), and sedation (10.0%). The incidence rates for the total AEs and the individual AEs were less in the **Update safety database** than in the original 120-Day Safety database in general.

Table 7-5 The Most Frequent (≥5%) AEs Reported in All (Controlled and Open-Label) Phase 2/3 ER Trials

Treatment group	Oxymorphone ER			Placebo		
Database	120-Day	Update [a]	Overall	120-Day	Update [a]	Overall
Total # patients	(N = 1089)	(N = 972)	(N = 2011)	(N = 350)	(N = 172)	(N = 522)
MedDRA preferred term						
Any adverse experience	976 (89.6)	759 (78.1)	1702 (84.6)	225 (64.3)	71 (41.3)	296 (56.7)
Nausea	500 (45.9)	213 (21.9)	711 (35.4)	63 (18.0)	10 (5.8)	73 (14.0)
Constipation	435 (39.9)	236 (24.3)	670 (33.3)	63 (18.0)	2 (1.2)	65 (12.5)
Dizziness (exc vertigo)	280 (25.7)	111 (11.4)	388 (19.3)	35 (10.0)	3 (1.7)	38 (7.3)
Vomiting NOS	256 (23.5)	91 (9.4)	346 (17.2)	23 (6.6)	2 (1.2)	25 (4.8)
Pruritus NOS	264 (24.2)	75 (7.7)	339 (16.9)	42 (12.0)	1 (0.6)	43 (8.2)
Somnolence	179 (16.4)	154 (15.8)	333 (16.6)	14 (4.0)	0 (0.0)	14 (2.7)
Headache NOS	129 (11.8)	104 (10.7)	233 (11.6)	26 (7.4)	2 (1.2)	28 (5.4)
Sweating increased	200 (18.4)	34 (3.5)	232 (11.5)	37 (10.6)	4 (2.3)	41 (7.9)
Sedation	188 (17.3)	14 (1.4)	202 (10.0)	37 (10.6)	0 (0.0)	37 (7.1)
Dry mouth	81 (7.4)	44 (4.5)	125 (6.2)	1 (0.3)	2 (1.2)	3 (0.6)
Insomnia NEC	62 (5.7)	55 (5.7)	117 (5.8)	8 (2.3)	2 (1.2)	10 (1.9)
Diarrhoea NOS	68 (6.2)	47 (4.8)	115 (5.7)	18 (5.1)	8 (4.7)	26 (5.0)
Fatigue	60 (5.5)	51 (5.2)	111 (5.5)	4 (1.1)	2 (1.2)	6 (1.1)
Appetite decreased NOS	54 (5.0)	24 (2.5)	78 (3.9)	1 (0.3)	1 (0.6)	2 (0.4)

[a] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
Note: AEs included in this table occurred in ≥5% of subjects in either column. This table is sorted by Overall Total frequency in descending order.
Source: Table 26 on pages 383 to 422.

A summary of the most frequent AEs (≥2%) from the ***placebo-controlled*** Phase 2/3 oxymorphone ER clinical trials is presented in the table below, which includes five controlled clinical trials (Studies 015, 016, 025, 031, and 032) with 1259 patients on oxymorphone ER and 461 on placebo. There were more reports of the total AEs and the most common individual AEs in the oxymorphone ER group than the placebo group for most of the AEs listed in the table.

Table 7-6 The Most Frequent (≥2%) AEs Reported in Placebo-Controlled Phase 2/3 ER Trials [a]

	Oxymorphone ER	Placebo	Total
Total # patients treated	(N = 1259)	(N = 461)	(N = 1720)
MedDRA preferred term			
Any adverse experience	1008 (80.1)	248 (53.8)	1256 (73.0)
Nausea	417 (33.1)	61 (13.2)	478 (27.8)
Constipation	347 (27.6)	61 (13.2)	408 (23.7)
Dizziness (exc vertigo)	224 (17.8)	35 (7.6)	259 (15.1)
Pruritus NOS	191 (15.2)	35 (7.6)	226 (13.1)
Somnolence	216 (17.2)	10 (2.2)	226 (13.1)
Vomiting NOS	196 (15.6)	19 (4.1)	215 (12.5)
Headache NOS	154 (12.2)	26 (5.6)	180 (10.5)
Sweating increased	108 (8.6)	40 (8.7)	148 (8.6)
Sedation	74 (5.9)	35 (7.6)	109 (6.3)
Dry mouth	80 (6.4)	3 (0.7)	83 (4.8)
Diarrhoea NOS	54 (4.3)	26 (5.6)	80 (4.7)
Insomnia NEC	50 (4.0)	9 (2.0)	59 (3.4)
Fatigue	49 (3.9)	6 (1.3)	55 (3.2)
Abdominal pain NOS	32 (2.5)	7 (1.5)	39 (2.3)
Appetite decreased NOS	36 (2.9)	2 (0.4)	38 (2.2)

[a] The Placebo Controlled Phase 2/3 ER Trials are: EN3202-015, EN3202-016, EN3202-025, EN3202-031 and EN3202-032.
Note: This table is sorted by total frequency in descending order.
Source: Table 28 on pages 436 to 448.

7.1.5.4 Common adverse event tables

Refer to the tables in the preceding section.

7.1.5.5 Identifying common and drug-related adverse events

The incidence rates of the most common drug-related (based on the Investigators' opinion) AEs occurring in ≥5% subjects in the oxymorphone ER Phase 2/3 studies are presented by preferred term (in descending frequency in the Overall database) in the table below. In the **Overall database**, the most frequently occurring drug-related AEs in patients treated with oxymorphone ER were constipation (32.8%), nausea (32.0%), dizziness (excluding vertigo, 18.1%), pruritus (16.1%), somnolence (16.0%), vomiting (14.3%), sweating increased (10.6%), and sedation (10.0%). The incidence rates for the total AEs and for the most common drug-related individual AEs were much less in the placebo group. There were fewer reports of drug- related AEs for the total AEs and the most common individual AEs in the **Update safety database** than in the original 120-Day Safety database.

Table 7-7 The Most Frequent (≥5%) Drug-Related AEs Reported in All Phase 2/3 ER Trials

Treatment group	Oxymorphone ER			Placebo		
Database	120-Day	Update	Overall	120-Day	Update	Overall
Total # patients	(N = 1089)	(N = 972)	(N = 2011)	(N = 350)	(N = 172)	(N = 522)
MedDRA preferred term						
Any adverse experience	870 (79.9)	595 (61.2)	1457 (72.5)	155 (44.3)	37 (21.5)	192 (36.8)
Constipation	431 (39.6)	229 (23.6)	659 (32.8)	62 (17.7)	2 (1.2)	64 (12.3)
Nausea	464 (42.6)	181 (18.6)	644 (32.0)	60 (17.1)	8 (4.7)	68 (13.0)

Dizziness (exc vertigo)	270 (24.8)	96 (9.9)	363 (18.1)	34 (9.7)	1 (0.6)	35 (6.7)
Pruritus NOS	253 (23.2)	70 (7.2)	323 (16.1)	36 (10.3)	0 (0.0)	36 (6.9)
Somnolence	171 (15.7)	150 (15.4)	321 (16.0)	12 (3.4)	0 (0.0)	12 (2.3)
Vomiting NOS	230 (21.1)	57 (5.9)	287 (14.3)	19 (5.4)	1 (0.6)	20 (3.8)
Sweating increased	193 (17.7)	23 (2.4)	214 (10.6)	36 (10.3)	2 (1.2)	38 (7.3)
Sedation	187 (17.2)	14 (1.4)	201 (10.0)	36 (10.3)	0 (0.0)	36 (6.9)
Headache NOS	83 (7.6)	63 (6.5)	146 (7.3)	14 (4.0)	1 (0.6)	15 (2.9)
Dry mouth	73 (6.7)	40 (4.1)	113 (5.6)	1 (0.3)	2 (1.2)	3 (0.6)

Source: Tables 20 and 21 on pages 35 and 36.

7.1.5.6 Additional analyses and explorations

Refer to the original NDA safety review.

7.1.6 Less Common Adverse Events

The incidence rates for most of the less common AEs were either similar or lower in the **Update Safety database** than the 120-Day safety database. The following AEs had noticeably higher percentage of reports in the Update Safety database than the 120-Day safety database: lethargy, upper abdominal pain, anemia, anorexia, flushing, peripheral edema, pain in extremity, hypotension, malignant neoplasm progression, asthenia, confusion state, pharyngolaryngeal pain, rash, generalized pruritus, gastroesophageal reflux disease, contusion, and neutropenia.

7.1.7 Laboratory Findings

There were no laboratory tests conducted in any of the new studies in the current submission. The safety concerns with the decreased WBC count, neutropenia, and LFT elevation had been addressed by the Sponsor in the submission (meeting package) dated February 17, 2004. Of the seven cases of low WBC and neutropenia, one had a less than 10% decrease and normal end-of-study values. The other six cases had abnormally low values due to laboratory sample mishandling. Three had repeated lab tests with the results within normal range and the other three were not available for laboratory retest. Of the five cases with abnormal LFT elevations, four had elevations at a post-operative setting and had concomitant medications and/or concurrent medical conditions known to increase liver enzymes. One had LFT and GGT elevation judged by the Investigator as unlikely related to the study drug. The Sponsor's explanations were considered acceptable by the Division as documented in the meeting minutes for the meeting held on March 16, 2004.

7.1.7.1 Overview of laboratory testing in the development program

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.7.3 Standard analyses and explorations of laboratory data

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.7.4 Additional analyses and explorations

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.7.5 Special assessments

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.8 Vital Signs

Vital signs were recorded in the Studies 031 and 032. The group mean changes in vital signs are summarized in the table below. Most of the changes in vital signs were fluctuations around the screening values. There was a trend of small decrease in systolic blood pressure in the first three weeks and small decrease in diastolic blood pressure in the first two weeks of the open-label treatment period in Study 031.

Table 7-8 Summary of Mean Change in Vital Signs

Treatment period	Open-label titration		Double-blind treatment		
Vital signs (VS)	Change in VS from screening			Change in VS from screening	
	Direction	Range		Direction	Range
Study 031			Treatment		
Systolic BP (mmHg)	↓	-3.3 to -6.7	Oxymorphone		-2.6 to 1.5
			Placebo	↓	-0.4 to -2.0
Diastolic BP (mmHg)	↓	-2.4 to -4.0	Oxymorphone		-0.7 to 0.5
			Placebo		-1.0 to 0.7
Heart rate (beat/min)		-0.1 to 1.4	Oxymorphone		-0.2 to 3.1
			Placebo		-0.5 to 1.7
Respiration rate (breath/min)		-0.1 to 0.0	Oxymorphone		-0.7 to 0.3
			Placebo		-0.1 to 0.4
Temperature (^{0}F)		0.1 to 0.2	Oxymorphone		0.0 to 0.1
			Placebo		0.0 to 0.1
Study 032					
Systolic BP (mmHg)	↓	-1.4 to -5.4	Oxymorphone		-2.6 to 2.1
			Placebo		-2.1 to 7.1
Diastolic BP (mmHg)	↓	-0.9 to -2.5	Oxymorphone		-0.8 to 1.7
			Placebo		-0.6 to 3.3
Heart rate (beat/min)	↑	0.3 to 1.7	Oxymorphone		-0.4 to 2.3
			Placebo	↑	2.7 to 4.8
Respiration rate (breath/min)		-0.2 to 0.2	Oxymorphone		-0.7 to 0.2
			Placebo		-0.7 to 0.1
Temperature (^{0}F)		0.0 to 0.1	Oxymorphone		-0.2 to 0.0
			Placebo		-0.2 to 0.1

Source: Tables 43 and 44 on pages 794-818 of the report of Study 031 and Tables 44 and 45 on pages 740-764 of the report of Study 032.

7.1.8.1 Overview of vital signs testing in the development program

Refer to section 7.1.8 and the safety review of the original NDA.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.8 and the safety review of the original NDA.

7.1.8.3 Standard analyses and explorations of vital signs data

Refer to section 7.1.8 and the safety review of the original NDA.

7.1.8.4 Additional analyses and explorations

Refer to section 7.1.8 and the safety review of the original NDA.

7.1.9 Electrocardiograms (ECGs)

There were no new ECG data in the current submission. According to the original NDA review there was a safety concern with QTc abnormality identified as QTc interval ≥430 msec (males) or 450 msec (females) or a change from pre-dose of ≥30 msec reported in 11 subjects from three Phase 1 clinical trials, Studies 001, 002, and 003.

Of the 11 subjects identified four had abnormalities at baseline with no worsening on treatment. QTc abnormalities for the other seven subjects are listed in the table below. The QTc abnormalities identified after treatment with oxymorphone 20 mg tablets in the first treatment period in **Subjects 1, 2, and 5** resolved upon rechallenge with the same formulation given in the subsequent period. The QTc abnormality identified following the treatment with oxymorphone 10 mg oral solution in the third treatment period in **Subject 7** resolved upon rechallenge with the 20 mg tablet treatment given in the fourth period. For **Subject 6**, the increase in QTc interval from 328 msec to 393 msec with 10 mg oral solution in the first treatment period did not continue upon the rechallenge with the same formulation in the second treatment period, where QTc interval was stabilized from a pre-dose value of 386 msec to a post-dose value of 385 msec. The length of the QTc interval fluctuated in an irregular pattern in the range of 367 msec and 473 msec during the three periods of treatment for **Subject 3**, for whom the abnormalities identified were a 43 msec increase from a pre-dose value of 404 msec to a post-dose value of 447 msec. Similarly, the length of the QTc interval fluctuated in an irregular pattern in the range of 382 msec and 413 msec during the four periods of treatment for **Subject 4**, for whom the abnormalities identified were the 30 msec (borderline) increase from a pre-dose value of 382 msec to a post-dose value of 412 msec. Also, all of the values for the QTc interval at the end of crossover treatments were <430 msec for six of the seven subjects.

The data did not suggest a causal relationship between the oxymorphone treatment and prolongation of QTc interval in this reviewer's opinion.

Table 7-9 Summary of QTc Interval Data: EN3202-002 and EN3202-003

				QTc (msec)		
	Subject ID	Period	Oxymorphone Treatment	Predose	Postdose	Reason for Abnormality
1	EN3202-002-001-001	1	20 mg tablet	372	476	Postdose ≥430 msec
		2	20 mg tablet	439	347	
		3	10 mg oral solution	387	364	
2	EN3202-002-001-006	1	20 mg tablet	358	491	Postdose ≥430 msec and increase from predose ≥30 msec
		2	20 mg tablet	374	356	
		3	10 mg oral solution	388	336	
3	EN3202-002-001-009	1	10 mg oral solution	408	367	
		2	20 mg tablet	473	419	
		3	20 mg tablet	404	447	Postdose ≥430 msec and increase from predose ≥30 msec
4	EN3202-003-001-002	1	20 mg tablet	386	390	
		2	20 mg tablet	382	412	Increase from predose ≥30 msec
		3	10 mg oral solution	396	391	
		4	10 mg oral solution	396	413	
5	EN3202-003-001-005	1	20 mg tablet	421	433	Postdose ≥430 msec
		2	10 mg oral solution	470	442	
		3	20 mg tablet	392	378	
		4	10 mg oral solution	388	376	

6	EN3202-003-001-012 [a]	1	10 mg oral solution	328	393	Increase from predose ≥30 msec
		2	10 mg oral solution	386	385	
7	EN3202-003-001-027	1	10 mg oral solution	352	352	
		2	20 mg tablet	342	356	
		3	10 mg oral solution	374	426	Increase from predose ≥30 msec
		4	20 mg tablet	362	358	

[a] Subject discontinued early.
Source: Table 5 on page 3746 of the safety update report.

The Sponsor performed a retrospective reanalysis of partially recollected data (not collected in the case report forms of the original submission) from Studies 015, 020, and 025 that provided the following findings though the interpretation of data was greatly limited by incomplete data and poor data quality.

- The incidences of on-study QTc prolongation judged by a baseline value of ≥430/450 msec or an increase from baseline by ≥30 msec, and on-study value of ≥500 msec were similar in the oxymorphone, oxycodone, and placebo treatment groups.

- Nearly 50% of all subjects had on-study shortening of the QTc interval (ranging from -1 to -270 msec), and about 20% who had baseline QTc prolongation of ≥ 430/450 msec subsequently had on-study QTc shortening in each treatment group.

- Of the four subjects identified as having an on-study QTc prolongation of ≥500 msec, one received placebo and three received oxymorphone treatment. Of the oxymorphone-treated patients Subject EN3202-025-011-010, had an increase from 392 msec at baseline to 505 msec at the end of the 2-week study with no cardiac AE. Subject EN3202-015-077-025 had an increase from 438 msec at baseline to 518 msec after four weeks of treatments and recovery to baseline level during the 1-year extended treatment. Subject EN3202-017-008-006 was hospitalized for an evaluation of myocardial ischemia in Study 017, who was subsequently enrolled in Study 020 and was found to have an increase from 425 msec to 501 msec after 17 days of extended treatment.

The data again did not suggest an association between the oxymorphone treatment and prolongation of QTc interval.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Refer to section 7.1.9 and the safety review of the original NDA.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.9 and the safety review of the original NDA.

7.1.9.3 Standard analyses and explorations of ECG data

Refer to section 7.1.9 and the safety review of the original NDA.

7.1.9.4 Additional analyses and explorations

Refer to section 7.1.9 and the safety review of the original NDA.

7.1.10 Immunogenicity

No data were available.

7.1.11 Human Carcinogenicity

There were no long-term exposure data for evaluation of human carcinogenicity.

7.1.12 Special Safety Studies

Dose dumping of oxymorphone by co-administration with alcohol was suggested by *in vivo* alcohol interaction study but not confirmed by *in vitro* dissolution test (refer to the PK review for detail).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The potential for drug abuse and dependence/withdrawal was evaluated in the safety review of the original submission and in the consultation from the Controlled Substances Staff. Two new studies (031 and 032) in the **Update Safety database** included two scales to measure withdrawal, the Clinical Opiate Withdrawal Scale (COWS) and the Adjective Rating Scale for Withdrawal (ARS). No signs of opiate withdrawal were suggested for the two treatments (oxymorphone and placebo) based on the mean COWS total score and the mean ARS total score at each visit during the double-blind treatment period for the all-treated-patient population. Similar results were seen for the subpopulation consisting of patients who discontinued for lack of efficacy, patients who discontinued due to all other reasons, and patients who completed the study. There were eight cases of discontinuation due to opioid withdrawal symptoms in the double-blind treatment period, including one oxymorphone-treated patient and two placebo patients in Study 031 and five placebo patients in Study 032.

7.1.14 Human Reproduction and Pregnancy Data

One case of on-study pregnancy was reported in Study 032. Patient EN3202-032-040-013 received 17 days of open-label oxymorphone ER treatment and then was discontinued from the trial due to a positive pregnancy test. Subsequent to her termination from the trial, the Principal Investigator notified the Sponsor that the patient had an elective abortion.

Refer to pharmacology/toxicology review for the studies of genotoxicity.

7.1.15 Assessment of Effect on Growth

There were no pediatric studies.

7.1.16 Overdose Experience

There were no reports of overdose in the **Update safety database**. Refer to the safety review of the original submission for the evaluation of overdose.

7.1.17 Postmarketing Experience

The extended-release oral formulation has not been approved for marketing in the U.S. or abroad. Oxymorphone IR approved in 1959 was removed from the market for commercial reasons. The 2 mg and 5 mg tablets were removed after seven years of marketing and the 10 mg tablet was removed after 11 years of marketing. The search for the postmarketing reports on available formulations only revealed 37 unique cases in AERS database in patients treated with intravenous and suppository formulations, which were discussed in the safety review of the original submission.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical safety data source was the **Update Safety database** consisting of data from subjects in the two trials (Studies 021 and 022) ongoing and four trials (Studies 028, 029, 031, and 032) planned at the time of the 120-Day Safety data cutoff date. The safe data from the120-Day Safety database were described and analyzed in the first cycle review of the original NDA submission. The Overall Safety database included the 120-Day Safety database and the Update Safety database. Safety data from the three safety populations (120-Day, Update, and Overall) will be listed side by side, wherever applicable for comparison purpose.

7.2.1.1 Study type and design/patient enumeration

The **Update Safety database** consisted of data from the following studies: two titration-to-effect, withdrawal design efficacy studies (031 and 032), two open-label safety studies (028 and 029), and two open-label extension studies (021 and 022) which were ongoing at the data cutoff date of the 120-Day Safety Update. As summarized in the table below the data set included a total of 971 patients, 575 patients in the two 16-week efficacy studies, 126 patients in the six-month open-label Study 028, 221 patients in the 12-month open-label Study 029, 38 of the 239 patients treated in Study 021, and 12 of the 24 patients treated in Study 022.

Table 7-10 Overview of Study Type and Design and Patient Enumeration

Protocol # Investigator(s)	Type	Design	Dates of Study	Dosage	# of subj	Demography Mean age (y) (range) Gender (M, F) Race (W, NW)
EN3202-031 31 sites	Dose ranging efficacy study in opioid-naïve patients with chronic low back pain	Open-label titration followed by randomized, double-blind, placebo-controlled	11/24/04-7/18/05	Titration to optimal doses of OM ER and then OM ER or Placebo	325	50.1 (18-85) 160 M, 165 F 289 W, 36 NW
EN3202-032 30 sites	Dose ranging efficacy study in patients with chronic low back pain	Open-label titration followed by randomized withdrawal, double-blind, placebo-controlled	10/13/04-8/19/05	Titration to optimal doses OM ER ≥20mg and then OM ER or Placebo	250	49.1 (21-85) 118 M, 132 F 219 W, 31 NW
EN3202-028 29 sites	Safety study in opioid-naïve patients with chronic pain	Multi-center, open-label	6/11/03-1/21/04	OM ER 5mg tab OM ER 10mg tab OM ER 20mg tab	126	56.2 (19-84) 55 M, 71 F 112 W, 14 NW
EN3202-029 40 sites	Safety study in patients with cancer or neuropathic pain	Multi-center, open-label	8/22/03-3/5/05	OM ER 5mg tab OM ER 10mg tab OM ER 20mg tab OM ER 40mg tab	221	56.8 (19-85) 123 F, 98 M 202 W, 19 NW
EN3202-021 44 sites	Safety study in adults with cancer pain or chronic lower back pain	Multi-center, open-label	3/14/01-7/2/03	Completed studies 016 & 019; Dose titration in the first week	239	48.0 (24-81) 128 M, 111 F 221 W, 18 NW

EN3202-022 25 sites	Safety study in cancer patients with moderate to severe pain	Multi-center, open-label	4/19/01-12/31/02	Completed study 018; Starting dosage from previous controlled-study; Dose titration	24	57.0 (36-71) 19 F, 5 M 21 W, 3 NW

Source: Supplemental Table 1 on pages 61 to 69 of the updated safety report.

7.2.1.2 Demographics

In the **Overall database** the mean age of the subjects in the Phase 2/3 ER studies was about 55 years. Slightly over one quarter of these subjects were elderly (65 years of age or older) and close to 10% were 74 years of age or older. Slightly more than one half of the subjects were female and most (close to 90%) of the subjects were Caucasian. The oxymorphone ER and placebo groups had very similar distributions of demographic characteristics. Subjects in the **Update database** had younger mean age and smaller proportion of the elderly patients, and lighter weight than subjects in the 120-Day safety database. The differences were more noticeable in the placebo group. Also, more male patients received placebo treatment than female patients in the Update database.

Table 7-11 Overall Demographics for Subjects in Phase 2/3 Oxymorphone ER Trials

Treatment	Oxymorphone ER			Placebo		
Database	120-Day	Update	Overall	120-Day	Update	Overall
# of patients	(N = 1089)	(N = 972)	(N = 2011)	(N = 350)	(N = 172)	(N = 522)
Age (yrs)						
N	1089	922	2011	350	172	522
Mean	57.4	52.3	55.1	58.9	47.2	55.1
Std	12.76	13.91	13.55	12.35	11.96	13.39
Min, max	24, 89	18, 85	18, 89	26, 93	20, 76	20, 93
< 65 years	731 (67.1)	744 (80.7)	1475 (73.3)	220 (62.9)	159 (92.4)	379 (72.6)
≥ 65 years	358 (32.9)	178 (19.3)	536 (26.7)	130 (37.1)	13 (7.6)	143 (27.4)
≥74 years	121 (11.1)	73 (7.9)	194 (9.6)	44 (12.6)	3 (1.7)	47 (9.0)
Gender, n (%)						
Female	619 (56.8)	491 (53.3)	1110 (55.2)	206 (58.9)	74 (43.0)	280 (53.6)
Male	470 (43.2)	431 (46.7)	901 (44.8)	144 (41.1)	98 (57.0)	242 (46.4)
Race, n (%)						
Asian	1 (0.1)	2 (0.2)	3 (0.1)			
Black	93 (8.5)	72 (7.8)	165 (8.2)	29 (8.3)	10 (5.8)	39 (7.5)
Caucasian	968 (88.9)	822 (89.2)	1790 (89.0)	313 (89.4)	155 (90.1)	468 (89.7)
Other	27 (2.5)	26 (2.8)	53 (2.6)	8 (2.3)	7 (4.1)	15 (2.9)
Height (in)						
N	1075	569	1644	350	172	522
Mean	66.7	67.3	66.9	66.6	67.6	66.9
Std	4.29	4.38	4.33	3.81	4.67	4.14
Min, max	48, 78	52, 91	48, 91	59, 78	52, 91	52, 91
Weight (lbs)						
N	1079	571	1650	350	172	522
Mean	198.6	193.4	196.8	202.4	188.2	197.7
Std	51.64	45.42	49.62	50.14	42.54	48.19
Min, max	84, 427	95, 383	84, 427	110, 425	95, 334	95, 425

Source: Tables 9 and 10 on pages 23 and 24 of the updated safety report.

7.2.1.3 Extent of exposure (dose/duration)

The total exposure in the Phase 2/3 ER trials consisted of about 2500 patients exposed to oxymorphone ER, or about 2000 to oxymorphone ER treatment and about 500 to placebo treatment categorized by their last

dose received in the study, in the Overall database. The information on the cumulative exposure to oxymorphone ER in the five open-label Phase 2/3 ER trials is presented in the table below. Overall, approximately 54% of the subjects (433/804) who participated in the open-label extension trials remained on study for six months, and 33% of the subjects (267/804) remained on study through Month 12. A total of 433 subjects had at least six months of exposure and 267 subjects had at least 12 months of exposure in these open-label studies.

Table 7-12 Extent of Cumulative Exposure in Open-Label Phase 2/3 Oxymorphone ER Trials

	Months on treatment [a]					
	3 Months	6 Months	9 Months	12 Months	18 Months	≥24 Months
Study (duration)	Number (%) of subjects on treatment					
020 (2-year)	197 (100)	104 (52.8)	94 (47.7)	86 (43.7)	42 (21.3)	26 (13.2)
021 (1-year)	239 (100)	160 (66.9)	126 (52.7)	111 (46.4)	3 (1.3)	0 (0.0)
022 (1-year)	24 (100)	9 (37.5)	7 (29.2)	7 (29.2)	7 (29.2)	1 (4.2)
028 (6-month)	124 (100)	63 (50.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
029 (1-year)	220 (100)	97 (44.1)	74 (33.6)	63 (28.6)	0 (0.0)	0 (0.0)
Total	804 (100)	433 (53.9)	301 (37.4)	267 (33.2)	52 (6.5)	27 (3.4)

[a] No dosing information was available for three patients (two in Study 028, one in Study 029) and therefore, they were excluded from this table.
Note: total exposure to oxymorphone was calculated on a per patient basis regardless of dose or changing doses for a patient within a study.
Source: Table 6 on page 20 of the updated safety report.

The information on the extent of exposure to oxymorphone ER treatment by modal daily dose category (the most frequent dose the patient took) and duration of treatment (of the most frequent dose) is summarized in the table below. The modal daily doses taken by subjects in the Phase 2/3 oxymorphone ER studies were in the following descending frequency: >10 to 50 mg/day in 57% of subjects (N=1129), >90 mg/day in 18% of subjects (N=349), >50 to 90 mg/day in 17% of subjects (N=336), and ≤10 mg/day in 9% of subjects (N=179).

There were 371 patient-years of exposure to oxymorphone ER in the Phase 2/3 oxymorphone ER studies. The majority of these patient-years were in the >10 to 50 mg/day modal daily dose category (163.4 patient-years), the >90 mg/day category (102.9 patient-years), and the >50 to 90 mg/day category (92.4 patient-years).

Table 7-13 Extent of Exposure by Treatment Duration and Modal Daily Dose–Phase 2/3 ER Trials

	Oxymorphone ER dosage (mg/day) [a]				
	≤10	>10-50	>50-90	>90	Total
Duration [b]	Number (%) of subjects on treatment				
1 - 3 Days	65 (18.8)	238 (69)	19 (5.5)	23 (6.7)	345 (100)
4 - 10 Days	67 (10.9)	332 (54.2)	118 (19.3)	95 (15.5)	612 (100)
11 - 17 Days	14 (5.8)	195 (81.3)	20 (8.3)	11 (4.6)	240 (100)
18 - 24 Days	2 (3.3)	40 (65.6)	11 (18)	8 (13.1)	61 (100)
25 - 31 Days	2 (6.9)	16 (55.2)	7 (24.1)	4 (13.8)	29 (100)
3 Months	13 (3.8)	173 (50.3)	72 (20.9)	86 (25)	344 (100)
6 Months	16 (10.1)	54 (34)	29 (18.2)	60 (37.7)	159 (100)
9 Months	0 (0.0)	15 (24.2)	21 (33.9)	26 (41.9)	62 (100)
12 Months	0 (0.0)	45 (45)	25 (25)	30 (30)	100 (100)
> 12 Months	0 (0.0)	21 (51.2)	14 (34.1)	6 (14.6)	41 (100)
> 18 Months	0 (0.0)	7 (58.3)	4 (33.3)	1 (8.3)	12 (100)
Total	179 (9)	1129 (56.6)	336 (16.9)	349 (17.5)	1993 (100)
Patient Years [c]	12.21	163.42	92.35	102.88	370.87

[a] No dosing information is available for two patients in Study 028, one patient in Study 029, nine patients in Study 031, and six patients in Study 032 and they are therefore excluded from this table.
[b] Total duration of exposure for all trials in which a patient participated.

[c] Patient years: the total number of days in a given modal dose group divided by 365.25.
Note: The information in the table represented the exposure to oxymorphone over time based on the most frequent dose the patient took, not each patient's total exposure.
Source: Table 7 on page 21 of the updated safety report.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Refer to the review of the original NDA.

7.2.2.1 Other studies

None.

7.2.2.2 Postmarketing experience

None.

7.2.2.3 Literature

Literature reports were reviewed in the safety review of the original submission. There were no new reports of AEs according to the Sponsor's most recent review of clinical literature.

7.2.3 Adequacy of Overall Clinical Experience

The number of subjects exposed to long-term treatment and the length of exposure appear sufficient for an adequate overall safety assessment. The level of exposure varied because of the changing dose with individual response and tolerance. The safety concerns with diagnostic laboratory test results and ECG findings from the original review were addressed in the meeting with the Division and in the current submission. The safety findings were in general expected of opioid treatment. The amount of controlled safety data was minimal, which makes the detection of new safety signals almost impossible.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Non-clinical studies were considered adequate according to the pharmacology/toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

Refer to the safety review of the original NDA.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Metabolic, clearance, and interaction workup were considered adequate according to the clinical pharmacology reviewer.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The safety database appears to have captured most of the expected opioid-related AEs.

7.2.8 Assessment of Quality and Completeness of Data

DSI inspection discovered inadequate, inaccurate, and inconsistent data reporting in a few cases mainly involving efficacy data. The entire dataset for the treatment-emergent AEs classified as "treatment-related" was not submitted until the information was requested by the reviewer.

7.2.9 Additional Submissions, Including Safety Update

There have been no further safety updates.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most frequently occurring AEs in patients treated with oxymorphone ER were nausea (35%), constipation (33%), dizziness (excluding vertigo, 19%), vomiting (17%), pruritus (17%), somnolence (17%), headache (12%), sweating increased (12%), and sedation (10%) in all Phase 2/3 studies (controlled and open-label studies) as well as in the placebo-controlled trials in the Overall database. The same set of symptoms was identified as the most common treatment-related AEs and most common AEs causing dropouts in the study. The incidence rates for these AEs were much lower in the placebo group. All these are known AEs associated with the use of opioid drugs.

The available data did not suggest treatment-related QTc prolongation or cardiac toxicity based on the findings of QTc back to normal range upon rechallenge and at the end of crossover treatment in the majority of cases reviewed and the review of serious cardiac AEs.

There was no notable safety signal for treatment-related decrease in WBC and neutrophil count (other than problems with laboratory sample mishandling) or LFT elevation.

The major limitation is the lack of controlled data, especially placebo-controlled long-term exposure from studies of a parallel design in the overall safety database. The data from open-label studies using historical controls had limited values in identifying new safety signals. In deciding the causality of a particular AE there is a tendency to attribute the cause of AE to the treatment if it has a commonly recognized association with the drug class and attribute the cause of AE to the concomitant medications and/or concurrent illness if it is not a known effect of the drug class.

Oxymorphone ER has a similar safety profile as the other opioid drugs and is considered reasonably safe to be used for the treatment of chronic pain with a careful initial dose titration to meet individual's acceptance of tolerance in a patient population not at high risks for the treatment.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data versus individual study data

Of the six studies in the **Update Safety database** four studies (028, 029, 021, and 022) had no control groups for comparison and two studies (031 and 032) had a placebo-control group withdrawing from oxymorphone treatment in a study population highly selected for their response and tolerance to the initial oxymorphone treatment. The only noticeable treatment differences between the oxymorphone treatment

group and placebo group in Study 031 (about 100 subjects per group) were more reports of nausea (12 versus nine), vomiting (eight versus one), constipation (sever versus one), dizziness (five versus three), headache (four versus two), and total number of AEs (58% versus 44%) in the active treatment arm than placebo arm. There were only one or two reports of any individual AE in patients receiving continued oxymorphone ER treatment during the double-blind treatment period in Study 032 (about 70 subjects per arm). Therefore, the individual study data had a very limited value for adequate evaluation of safety.

7.4.1.2 Combining data

The safety data from all Phase 2/3 trials are combined and grouped by the 120-Day safety database already reviewed before, the Update safety database with the new information, and the Overall safety database combining the two.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Refer to the safety review of the original NDA.

7.4.2.2 Explorations for time dependency for adverse findings

Refer to the safety review of the original NDA.

7.4.2.3 Explorations for drug-demographic interactions

Incidence rates for all treatment-emergent AEs occurring in 5% or more of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER trials are presented by age group in the table below.
In the **Overall database** there were larger percentages of reports of nausea, dizziness (exc vertigo), vomiting, somnolence, dry mouth, fatigue, and appetite decreased in the elderly group than in the younger age group. There appeared to be an age-related increase in incidence rates of dizziness and somnolence. On the other hand, the percentages of reports of pruritus, headache, sweating increased, and sedation were lower in the elderly group than in the younger age group. The incidence rates in the **Update safety database** were much lower than what were reported in the 120-Day safety database for majority of the most commonly occurring individual AEs for all the age groups.

Table 7-14 The Most Frequent (≥5%) AEs by Age Group and Preferred Term in Phase 2/3 ER Trials

	120-Day Safety Total (N=1089)			Update Total [b] (N=972)			Overall Total (N=2011)		
Age group [a]	Age < 65	Age ≥65	Age ≥74	Age < 65	Age ≥65	Age ≥74	Age < 65	Age ≥65	Age ≥74
# of subjects	731	358	121	789	183	74	1475	536	194
Any AE	649 (88.8)	327 (91.3)	110 (90.9)	598 (75.8)	161 (88.0)	65 (87.8)	1219 (82.6)	483 (90.1)	174 (89.7)
Nausea	322 (44.0)	178 (49.7)	60 (49.6)	165 (20.9)	48 (26.2)	21 (28.4)	485 (32.9)	226 (42.2)	81 (41.8)
Constipation	299 (40.9)	136 (38.0)	42 (34.7)	179 (22.7)	57 (31.1)	26 (35.1)	477 (32.3)	193 (36.0)	68 (35.1)
Dizziness (exc vertigo)	177 (24.2)	103 (28.8)	42 (34.7)	78 (9.9)	33 (18.0)	16 (21.6)	252 (17.1)	136 (25.4)	58 (29.9)
Vomiting NOS	163 (22.3)	93 (26.0)	32 (26.4)	69 (8.7)	22 (12.0)	8 (10.8)	231 (15.7)	115 (21.5)	40 (20.6)
Pruritus NOS	204 (27.9)	60 (16.8)	22 (18.2)	60 (7.6)	15 (8.2)	6 (8.1)	264 (17.9)	75 (14.0)	28 (14.4)
Somnolence	106 (14.5)	73 (20.4)	35 (28.9)	121 (15.3)	33 (18.0)	13 (17.6)	227 (15.4)	106 (19.8)	48 (24.7)
Headache NOS	100 (13.7)	29 (8.1)	8 (6.6)	92 (11.7)	12 (6.6)	3 (4.1)	192 (13.0)	41 (7.6)	11 (5.7)
Sweating ↑	160 (21.9)	40 (11.2)	10 (8.3)	25 (3.2)	9 (4.9)	3 (4.1)	184 (12.5)	48 (9.0)	13 (6.7)
Sedation	153 (20.9)	35 (9.8)	7 (5.8)	12 (1.5)	2 (1.1)	1 (1.4)	165 (11.2)	37 (6.9)	8 (4.1)

Dry mouth	46 (6.3)	35 (9.8)	12 (9.9)	37 (4.7)	7 (3.8)	4 (5.4)	83 (5.6)	42 (7.8)	16 (8.2)
Insomnia NEC	43 (5.9)	19 (5.3)	10 (8.3)	46 (5.8)	9 (4.9)	5 (6.8)	89 (6.0)	28 (5.2)	15 (7.7)
Diarrhoea NOS	50 (6.8)	18 (5.0)	6 (5.0)	39 (4.9)	8 (4.4)	4 (5.4)	89 (6.0)	26 (4.9)	10 (5.2)
Fatigue	39 (5.3)	21 (5.9)	9 (7.4)	37 (4.7)	14 (7.7)	8 (10.8)	76 (5.2)	35 (6.5)	17 (8.8)
Appetite ↓ NOS	29 (4.0)	25 (7.0)	9 (7.4)	17 (2.2)	7 (3.8)	4 (5.4)	46 (3.1)	32 (6.0)	13 (6.7)
Pyrexia	37 (5.1)	14 (3.9)	4 (3.3)	15 (1.9)	5 (2.7)	2 (2.7)	51 (3.5)	19 (3.5)	6 (3.1)

[a] Age of subject from subject youngest recorded age. This table is sorted by Overall Total frequency in descending order.
[b] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
Source: Table 27 on page 45 of the updated safety report.

Incidence rates for all treatment-emergent AEs occurring in 5% or more of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER trials are presented by gender in the table below.
In the **Overall database** there were larger percentage of reports of nausea, vomiting, pruritus, headache, and dry mouth, in female than male patients. The pattern in the **Update safety database** was the same. The incidence rates in the Update safety database were much lower than what were reported in the 120-Day safety database for majority of the most commonly occurring individual AEs for both genders.

Table 7-15 The Most Frequent (≥5%) AEs by Gender and Preferred Term in Phase 2/3 ER Trials

	120-Day Safety Total		Update Total [a]		Overall Total	
	(N=1089)		(N=972)		(N=2011)	
	Male	Female	Male	Female	Male	Female
Number of Subjects	470	619	453	519	901	1110
Any Adverse Experience	404 (86.0)	572 (92.4)	344 (75.9)	415 (80.0)	736 (81.7)	966 (87.0)
Nausea	181 (38.5)	319 (51.5)	67 (14.8)	146 (28.1)	248 (27.5)	463 (41.7)
Constipation	197 (41.9)	238 (38.4)	112 (24.7)	124 (23.9)	309 (34.3)	361 (32.5)
Dizziness (exc vertigo)	116 (24.7)	164 (26.5)	51 (11.3)	60 (11.6)	166 (18.4)	222 (20.0)
Vomiting NOS	78 (16.6)	178 (28.8)	34 (7.5)	57 (11.0)	112 (12.4)	234 (21.1)
Pruritus NOS	106 (22.6)	158 (25.5)	23 (5.1)	52 (10.0)	129 (14.3)	210 (18.9)
Somnolence	69 (14.7)	110 (17.8)	68 (15.0)	86 (16.6)	137 (15.2)	196 (17.7)
Headache NOS	36 (7.7)	93 (15.0)	39 (8.6)	65 (12.5)	75 (8.3)	158 (14.2)
Sweating increased	87 (18.5)	113 (18.3)	19 (4.2)	15 (2.9)	106 (11.8)	126 (11.4)
Sedation	85 (18.1)	103 (16.6)	3 (0.7)	11 (2.1)	88 (9.8)	114 (10.3)
Dry mouth	24 (5.1)	57 (9.2)	16 (3.5)	28 (5.4)	40 (4.4)	85 (7.7)
Insomnia NEC	23 (4.9)	39 (6.3)	30 (6.6)	25 (4.8)	53 (5.9)	64 (5.8)
Diarrhoea NOS	24 (5.1)	44 (7.1)	21 (4.6)	26 (5.0)	45 (5.0)	70 (6.3)
Fatigue	28 (6.0)	32 (5.2)	20 (4.4)	31 (6.0)	48 (5.3)	63 (5.7)
Appetite decreased NOS	22 (4.7)	32 (5.2)	13 (2.9)	11 (2.1)	35 (3.9)	43 (3.9)

[a] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
Note: This table is sorted by Overall Total frequency in descending order.
Source: Table 29 on page 49 of the updated safety report.

In the **Overall database** only 165 of the 2011 (8.2%) subjects were African American and 56 of 2011 (2.8%) were classified as others. The safety data were mainly from the Caucasian population, which accounted for about 90% of the study population. Therefore, the discussion about drug-demographic interactions with respect to race is limited because of the dramatic imbalance in subpopulation size. Nevertheless, the incidence rates for all treatment-emergent AEs occurring in 5% or more of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER trials are presented by racial group in the table below. In the Overall database the incidence rates for dizziness (exc vertigo), somnolence, and sedation appeared to be higher in Caucasian study population than in African American population. The incidence rates in the **Update safety database** were much lower than what were reported in the 120-Day safety database for some of most commonly occurring individual AEs for all the racial groups.

Table 7-16 The Most Frequent (≥5%) AEs by Racial Group and Preferred Term in Phase 2/3 ER Trials

	120-Day Safety Total			Update Total [a]			Overall Total		
	(N=1089)			(N=972)			(N=2011)		
	Caucasian	Black	Other	Caucasian	Black	Other	Caucasian	Black	Other
# of subjects	968	93	28	866	77	29	1790	165	56
Any AE	873 (90.2)	81 (87.1)	22 (78.6)	683 (78.9)	53 (68.8)	23 (79.3)	1526 (85.3)	131 (79.4)	45 (80.4)
Nausea	447 (46.2)	42 (45.2)	11 (39.3)	191 (22.1)	18 (23.4)	4 (13.8)	637 (35.6)	59 (35.8)	15 (26.8)
Constipation	397 (41.0)	27 (29.0)	11 (39.3)	221 (25.5)	11 (14.3)	4 (13.8)	617 (34.5)	38 (23.0)	15 (26.8)
Dizziness (exc Vertigo)	253 (26.1)	18 (19.4)	9 (32.1)	105 (12.1)	3 (3.9)	3 (10.3)	355 (19.8)	21 (12.7)	12 (21.4)
Vomiting NOS	227 (23.5)	26 (28.0)	3 (10.7)	79 (9.1)	9 (11.7)	3 (10.3)	306 (17.1)	34 (20.6)	6 (10.7)
Pruritus NOS	237 (24.5)	22 (23.7)	5 (17.9)	64 (7.4)	9 (11.7)	2 (6.9)	301 (16.8)	31 (18.8)	7 (12.5)
Somnolence	165 (17.0)	11 (11.8)	3 (10.7)	139 (16.1)	9 (11.7)	6 (20.7)	304 (17.0)	20 (12.1)	9 (16.1)
Headache NOS	115 (11.9)	8 (8.6)	6 (21.4)	96 (11.1)	7 (9.1)	1 (3.4)	211 (11.8)	15 (9.1)	7 (12.5)
Sweating ↑	183 (18.9)	11 (11.8)	6 (21.4)	30 (3.5)	3 (3.9)	1 (3.4)	211 (11.8)	14 (8.5)	7 (12.5)
Sedation	176 (18.2)	9 (9.7)	3 (10.7)	14 (1.6)	0 (0.0)	0 (0.0)	190 (10.6)	9 (5.5)	3 (5.4)
Dry mouth	74 (7.6)	6 (6.5)	1 (3.6)	39 (4.5)	4 (5.2)	1 (3.4)	113 (6.3)	10 (6.1)	2 (3.6)
Insomnia NEC	55 (5.7)	4 (4.3)	3 (10.7)	50 (5.8)	4 (5.2)	1 (3.4)	105 (5.9)	8 (4.8)	4 (7.1)
Diarrhoea NOS	61 (6.3)	4 (4.3)	3 (10.7)	42 (4.8)	2 (2.6)	3 (10.3)	103 (5.8)	6 (3.6)	6 (10.7)
Fatigue	53 (5.5)	6 (6.5)	1 (3.6)	46 (5.3)	5 (6.5)	0 (0.0)	99 (5.5)	11 (6.7)	1 (1.8)
Appetite ↓ NOS	48 (5.0)	4 (4.3)	2 (7.1)	22 (2.5)	1 (1.3)	1 (3.4)	70 (3.9)	5 (3.0)	3 (5.4)
Pyrexia	43 (4.4)	7 (7.5)	1 (3.6)	19 (2.2)	0 (0.0)	1 (3.4)	61 (3.4)	7 (4.2)	2 (3.6)
Arthralgia	36 (3.7)	4 (4.3)	2 (7.1)	22 (2.5)	1 (1.3)	0 (0.0)	58 (3.2)	5 (3.0)	2 (3.6)
Abdominal pain NOS	33 (3.4)	4 (4.3)	1 (3.6)	18 (2.1)	5 (6.5)	0 (0.0)	51 (2.8)	9 (5.5)	1 (1.8)
Influenza	31 (3.2)	4 (4.3)	2 (7.1)	18 (2.1)	0 (0.0)	0 (0.0)	49 (2.7)	4 (2.4)	2 (3.6)
Dyspepsia	21 (2.2)	3 (3.2)	2 (7.1)	26 (3.0)	1 (1.3)	1 (3.4)	47 (2.6)	4 (2.4)	3 (5.4)

[a] Subjects who either continued in one of the studies after the 120-Day Safety Update cut-off or subjects who experienced AEs not reported in the 120-Day Update (the AEs had to be new or had to have increased in severity from AEs previously reported) or were from studies EN3202-028, EN3202-029, EN3202-031 and EN3202-032.
Note: This table is sorted by Overall Total frequency in descending order.
Source: Table 31 on page 53 of the updated safety report.

7.4.2.4 Explorations for drug-disease interactions

Refer to the safety review of the original NDA.

7.4.2.5 Explorations for drug-drug interactions

Refer to the safety review of the original NDA.

7.4.3 Causality Determination

Most of the commonly occurring AEs were treatment-related AEs known to be associated with the use of opioid drugs. The data have limited values in identifying new safety signals due to the lack of controlled data of long-term exposure.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The efficacy and safety findings from the trials using titration to effect design support the proposed dosing regimen for opioid naïve patients, i.e., to initiate at 5 mg q12h followed by individualized titration at increments of 5-10 mg q12h every 3-7 days, to a level that provides adequate analgesia and minimizes side effects. The proposed conversion from other opioids in the dosing instruction for opioid experienced patients is not supported by data because the studies of relative potency between oxymorphone ER and other opioids had not provided useful information about the relative potency.

8.2 Drug-Drug Interactions

Refer to the safety review of the original NDA.

8.3 Special Populations

Elderly patients are at higher risk for oxymorphone treatment-related adverse events due to a higher level of systemic exposure (about a 40% increase in total and maximum drug levels in comparison to younger subjects). Elderly patients have been shown to have increased risks to oxymorphone-induced respiratory/CNS depression at higher starting doses in a post-operative setting based on the results of studies in the original submission. There was also an age-related increase in incidence rates of dizziness and somnolence. Therefore, there should be a lower starting doses, slower titration, and closer monitoring for the elderly patients.

8.4 Pediatrics

[redacted]

8.5 Advisory Committee Meeting

This 505(b)(2) application is not planned to be discussed at an Advisory Committee meeting.

8.6 Literature Review

Literature reports were reviewed in the safety review of the original submission. There were no new reports of AEs according to the Sponsor's most recent review of clinical literature.

8.7 Postmarketing Risk Management Plan

The Sponsor's proposed post-marketing Risk Management Plan (RMP) for oxymorphone products has been reviewed in detail in the consultation from the Office of Drug Safety (ODS). There have been several

communications with the Sponsor to address the concerns. To date most of the issues have been resolved. The additional recommendations from ODS include further education in patients and HCPs about the appropriate use of oxymorphone ER, the risk associated with inappropriate use, and the differences between the IR and ER formulations, strong warning against the use with alcohol and warning about starting at higher doses of oxymorphone ER in opioid naïve patients in the labeling, inclusion of any pediatric (age 16 years or younger) use or medication error in the 15-day Alert Report, and a number of other comments about the Sponsor's pharmacovigilance and educational plans in RMP. The consultation from the Controlled Substance Staff provided additional recommendations regarding the details and the use of data analysis instrument in risk management, and a number of labeling revisions.

8.8 Other Relevant Materials

The use of the proprietary name, OPANA^{TM} ER is considered acceptable by recommendations from the Division of Medication Errors and Technical Support.

9 OVERALL ASSESSMENT

9.1 Conclusions

Oxymorphone ER studied at individualized dosage in highly selected responders was shown to be efficacious in treating chronic low back pain based on the replicable positive findings from the studies of chronic low back pain.

Oxymorphone ER has a similar safety profile as the other opioid drugs and is considered reasonably safe to be used with a careful initial dose titration to meet individual's acceptance of tolerance, for the treatment of chronic pain in both opioid naïve and opioid experienced populations.

9.2 Recommendation on Regulatory Action

Oxymorphone ER is recommended for market approval.

9.3 Recommendation on Postmarketing Actions

None.

9.3.1 Risk Management Activity

The Sponsor's proposed post-marketing Risk Management Plan (RMP) for oxymorphone products is considered acceptable in general. The additional recommendations from the Office of Drug Safety and the Controlled Substance Staff will be forwarded to the Sponsor.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

There should be further studies of relative potency in comparison to the other commonly used opioids to well inform the labeling.

9.4 Labeling Review

The labeling will be reviewed separately.

9.5 Comments to Applicant

Further studies of relative potency in comparison to the other commonly used opioids should be conducted. Risk Management Plan should incorporate all the recommendations from the Office of Drug Safety and the Controlled Substance Staff.

10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Study 031

Protocol
Study EN3202-031 was planned as a titration-to-effect, randomized withdrawal, double-blind, placebo-controlled, parallel, multiple-dose, dose range study of chronic low back pain (LBP) in opioid naïve patients. The study was planned to have two periods: an open-label titration period and a double-blind, placebo-controlled treatment period.

Eligible subjects were going to be patients with moderate to severe chronic (≥3 months duration), non-neuropathic low back pain (LBP), with suboptimal response to non-opioid analgesic regimens, and without prior use of around-the-clock opioid (opioid naïve).

Following screening assessments all eligible patients were planned to be started on open-label treatments with two days (Day 1 and 2) of oxymorphone ER 5 mg q12 hours followed by upward titration at increments of 5 to10 mg q12 hours every three to seven days until reaching stabilization. To be eligible to enter the double-blind, placebo-controlled treatment, patients were going to be required to be stabilized within four weeks of open-label treatment. Stabilization was going to be defined as reaching a tolerated dose that would provide adequate pain relief, i.e., maintaining an average pain intensity score of ≤40 mm by visual analogue scale (VAS) for three of five consecutive days immediately prior to randomization, and reaching a minimum dose of oxymorphone ER of 10 mg q12 hours (20 mg daily) prior to randomization. No rescue medication was going to be allowed during the titration period. Patients requiring rescue were to be discontinued. Anti-constipation medication was planned to be available throughout the study.

Patients eligible for double-blind treatment were planned to be randomized to either continue on the stabilized dose of oxymorphone ER or replace oxymorphone ER treatment with placebo. During the 12-week double-blind treatment oxymorphone immediate release (IR) was going to be allowed as rescue pain medication for breakthrough pain and as an aid in tapering placebo patients to prevent opioid withdrawal. The use of rescue medication was planned as oxymorphone IR 5 mg q4-6h as needed during the first four days of double-blind treatment and at most twice daily thereafter. Patients who developed intolerance or inadequate pain control to their established dose of study drug were going to be terminated from the study. Patients were to be instructed to keep a daily diary record of the total oxymorphone ER (or placebo) dose, as well as any oxymorphone IR (rescue medication) dose. During the double-blind treatment period, patients were going to return to the site for safety and efficacy assessments at Day 4 and Weeks 1, 2, 3, 4, 6, 8, 10, and 12 (±3 days).

Efficacy was planned to be measured by the change in average pain intensity from baseline (last VAS pain score before randomization) to final study visit as the primary endpoint and by time to early discontinuation due to lack of efficacy and patient/physician global satisfaction with study medication as the secondary endpoints.

Safety and tolerability were planned to be evaluated by adverse events (AEs), vital signs, discontinuations due to drug-related AEs (tolerability), and investigator- and patient-rated signs and symptoms of opioid withdrawal.