

Clinical Trial Results Summary
 Study EN3203-010

Study Number: EN3203-010	
Title of Study: An Open-Label, Ascending, Two-Part, Single- and Multiple-Dose Evaluation of the Safety, Pharmacokinetics, and Effectiveness of Oxymorphone for Acute Postoperative Pain in Pediatric Subjects	
Principal Investigator: Multicenter Investigators: 10 investigators, all of whom enrolled subjects	
Study Center(s): 10 centers in the United States	
Publications (Reference): None	
Studied Period (Years): Date first patient enrolled: 17-Feb-2009 Date last patient completed: 18-Apr-2011	Phase of Development: Phase 3
<p>Objectives:</p> <p><i>Primary:</i></p> <ul style="list-style-type: none"> • <u>Single-Dose Period:</u> To determine the safety of oxymorphone immediate release (IR) in children aged >12 to 17 years requiring an opioid to treat their acute postoperative pain of various etiologies. • <u>Multiple-Dose Period:</u> To determine the effectiveness/clinical utility of oxymorphone IR in this subject population. <p><i>Secondary:</i></p> <ul style="list-style-type: none"> • To determine the pharmacokinetic profile of oxymorphone IR in this subject population; • To determine the appropriate dosing recommendations for oxymorphone IR in this subject population. 	
<p>Methodology: This open-label, 2-part, ascending-dose, multicenter study was designed to gain experience with a classic, single-dose and multiple-dose postoperative treatment paradigm utilizing oxymorphone IR tablets in >12 to 17 year old subjects (administrative change) with postoperative pain requiring an opioid. The original planned age group was 6 to 17. However, no subjects had been enrolled into the study prior to the administrative change. An external Data Safety Monitoring Board (DSMB) reviewed all individual and aggregate safety, effectiveness, and pharmacokinetic data prior to dose escalation within each study period. This study was conducted to fulfill a postmarketing commitment.</p> <p>Single-Dose Period</p> <p>Three (3) doses of oxymorphone IR were to be studied in ascending fashion (in stepwise order, based on the previous groups' demonstrated safety and tolerability): 5 mg, 10 mg, and 15 mg. The first group of subjects was to be given a single dose of oxymorphone IR 5 mg. With acceptable safety (as reviewed by the DSMB), the next group of subjects was to be dosed with oxymorphone IR 10 mg. If the 10-mg group demonstrated acceptable safety and tolerability, then the final group of subjects was to be administered oxymorphone IR 15 mg. If needed, rescue analgesia was available according to standard of care (SOC) at each institution.</p> <p>Study assessments occurred at the screening visit within 14 days of surgery, baseline (within 30 hours after surgery), and 15 and 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours after the dose. An end of study evaluation was to occur 24 hours after the dose or early termination.</p> <p>Multiple-Dose Period</p> <p>Up to 3 doses of oxymorphone were to be studied in ascending fashion (in stepwise order, based on previous groups' demonstrated safety/tolerability and effectiveness). Doses used in the multiple-dose period were determined from the results of the single-dose period. Following postoperative parenteral</p>	

Clinical Trial Results Summary
Study EN3203-010

<p>analgesia, when oral dosing commenced according to each institution's SOC (within 30 hours post-surgery), dosing was to begin at the lowest dose selected from the single-dose period. Subjects were to be dosed every 4 to 6 hours (no sooner than every 4 hours and no later than every 6 hours) for up to 48 hours. Subjects could receive rescue medication and discontinued in the event that the study medication did not continue to provide adequate pain relief. Dose escalation to the second and third higher doses was to commence once safety and effectiveness (as reviewed by the DSMB) had been determined at the lower dose.</p> <p>Study assessments occurred at the screening visit within 14 days of surgery, baseline (within 30 hours after surgery), and 15 and 30 minutes, 1, 2, 3, 4, 6, 8, 12, 24, 28, 32, and 36 hours after the first dose. An end of study evaluation was to occur 48 hours after the first dose or early termination.</p>
<p>Number of Patients (Planned and Analyzed):</p> <p><i>Planned:</i> 48 subjects total</p> <p><i>Safety population:</i> 58 subjects total (13 received 5-mg single dose, 9 received 10-mg single dose, 11 received 15-mg single dose, 9 received 5-mg multiple doses, 8 received 10-mg multiple doses, 8 received 15-mg multiple doses)</p> <p><i>Pharmacokinetic population:</i> 52 subjects total (11 received 5-mg single dose, 8 received 10-mg single dose, 9 received 15-mg single dose, 8 received 5-mg multiple doses, 8 received 10-mg multiple doses, 8 received 15-mg multiple doses)</p> <p><i>ITT Population:</i> 58 subjects total (13 received 5-mg single dose, 9 received 10-mg single dose, 11 received 15-mg single dose, 9 received 5-mg multiple doses, 8 received 10-mg multiple doses, 8 received 15-mg multiple doses)</p>
<p>Diagnosis and Main Criteria for Inclusion: Subjects aged >12 to 17 years with postoperative pain requiring an opioid.</p>
<p>Test Product, Dose and Mode of Administration, Batch Number: OPANA[®] (oxymorphone hydrochloride) for oral dosing supplied as 5-mg (lot numbers 400865NV and 401427NV) and 10-mg (lot numbers 400953NV and 401428NV) IR tablets.</p> <p><i>Single-Dose Period:</i> 5 mg, 10 mg, and 15 mg oxymorphone IR.</p> <p><i>Multiple-Dose Period:</i> 5 mg, 10 mg, and 15 mg. Dosing began at the lowest dose selected from the single-dose period.</p> <p>Rescue analgesia was available according to SOC at each institution.</p>
<p>Duration of Treatment:</p> <p><i>Single-Dose Period:</i> Within 30 hours after surgery, subjects developing a moderate level of pain as defined by a 100-mm visual analog scale (VAS) received 1 dose.</p> <p><i>Multiple-Dose Period:</i> Following postoperative parenteral analgesia, oral dosing commenced according to each institution's SOC (within 30 hours post-surgery) and was repeated every 4 to 6 hours (no sooner than every 4 hours and no later than every 6 hours) for up to 48 hours.</p>
<p>Reference Therapy, Dose and Mode of Administration, Batch Number: None</p>
<p>Criteria for Evaluation:</p> <p><i>Efficacy:</i> Assessments of current pain intensity using a 100-mm VAS obtained over a 6-hour period (single-dose period) or a 48-hour period (multiple-dose period) following dose administration, or until rescue medication is used.</p> <p><i>Safety:</i> Adverse events (AEs), respiratory function monitoring, neurological function monitoring, clinical laboratory tests, and vital signs.</p> <p><i>Pharmacokinetics:</i> Blood samples for pharmacokinetic assessments of oxymorphone obtained over a</p>

24-hour period (single-dose period) or a 48-hour period (multiple-dose period) following dose administration.

Statistical Methods: No inferential statistical tests were performed. Efficacy data were summarized by descriptive statistics. The pain intensity difference was calculated as the current pain intensity at each post-dose time point minus the current pain intensity score at baseline. Summary statistics of the pain intensity scores using VAS and change from baseline were presented by treatment group and study period for each time point.

The following pharmacokinetic variables were estimated from the plasma concentration data using standard non-compartmental methods: C_{max} , T_{max} , AUC_{0-t} , AUC_{0-inf} , λ , and $t_{1/2}$.

Summaries of AEs were presented by system organ class and preferred term. The occurrence of AEs was also tabulated by severity. Serious adverse events (SAEs) and AEs resulting in discontinuation were summarized separately. All laboratory results, vital sign measurements, and other safety variables were summarized by study period and treatment group for each time point using descriptive statistics or frequency distributions.

SUMMARY:

EFFICACY RESULTS:

In both the single-dose and multiple-dose periods, improvement in postoperative pain following pediatric surgery was seen in all treatment groups.

In the single-dose period, the mean pain intensity scores decreased (improved) from baseline at each time point in each of the 3 treatment groups. The largest mean change from baseline was seen at 4 hours post dose in the 5-mg group (mean [standard deviation (SD)] change of -36.2 [25.03]), 3 hours post dose in the 10-mg group (mean change of -29.3 [20.21]), and 2 hours post dose in the 15-mg group (mean change of -33.8 [20.10]).

In the multiple-dose period, the mean pain intensity scores improved from baseline at each time point following the first dose in each of the 3 treatment groups, except in the 10-mg group at 15 minutes and 30 minutes post first dose (mean [SD] changes of 0.5 [9.56] and 3.1 [22.33], respectively). The mean largest changes were seen in each dose group at 1 hour post first dose. In the multiple-dose period, pain intensity also improved from baseline to immediately prior to each subsequent dose (every 4 to 6 hours) in the 5-mg and 15-mg dose groups and immediately prior to each subsequent dose except doses 2, 3, and 4 following the first dose in the 10-mg group.

PHARMACOKINETICS RESULTS:

In the single-dose period, the total plasma exposure, AUC_{0-inf} , of both oxymorphone and 6-OH-oxymorphone increased with increasing dose. Between the 10-mg and 15-mg dose the mean AUC_{0-inf} of oxymorphone increased in a greater than dose proportional manner. However, due to the small number of subjects and the wide variability in the data, it is not possible to make any conclusive interpretation of this observation. The mean C_{max} of oxymorphone was lower in the 10-mg group versus the 5-mg group, which may be related to the small number of subjects and a high degree of intersubject variability. AUC_{0-inf} and C_{max} of 6-OH-oxymorphone, on the other hand, appeared to occur in a near proportional manner with oxymorphone dose. The mean half-life of oxymorphone increased with increasing dose from 12.1 hours in the 5-mg group to 15.9 hours in the 10-mg group and 20.0 hours in the 15-mg group. The half-life of 6-OH-oxymorphone, however, appeared to be independent of oxymorphone dose.

In the multiple-dose period of this study, pharmacokinetic parameters for oxymorphone and 6-OH-oxymorphone were not evaluated. Rather, their 4-hour plasma concentrations, which mostly represented trough levels from the subsequent dose, were analyzed.

There was a significant amount of variability in the concentration-time scatter plots, but in general there appeared to be a >2-fold increase in median oxymorphone and 6-OH-oxymorphone concentration within

Clinical Trial Results Summary
Study EN3203-010

each of the 3 dose groups following multiple oxymorphone dosing. In addition, the median oxymorphone plasma concentrations appeared to increase with dose in a nearly dose proportional manner.

SAFETY RESULTS:

Overall, treatment-emergent adverse events (TEAEs) were reported in 42.4% of subjects in the single-dose period, with the lowest incidence in the 5-mg group (23.1%) compared to 44.4% in the 10-mg group and 63.3% in the 15-mg group. During the single dose period, the most frequently reported TEAEs overall were nausea and pyrexia (4 subjects, 12.1% each) and constipation, hypoesthesia, and vomiting (2 subjects, 6.1% each). Overall, TEAEs were reported in 76.0% of subjects in the multiple-dose period, with the lowest incidence in the 10-mg group (62.5%) compared to 88.9% in the 5-mg group and 75.0% in the 15-mg group. During the multiple dose period, the most frequently reported TEAEs overall were constipation (8 subjects, 32.0%); nausea (7 subjects, 28.0%); oxygen saturation decreased, dizziness, urinary retention, anemia, and headache (4 subjects, 16.0% each); and pyrexia, vomiting, and pruritus (3 subjects, 12.0% each).

No deaths occurred. SAEs were reported for 2 subjects in the single-dose period (moderate intensity atelectasis and fat embolism in 1 subject in the 10-mg group and severe intensity implant failure in 1 subject in the 15-mg group) and 1 subject in the multiple-dose period (5-mg group moderate intensity unequal pupils, anemia, blurred vision, and headache). All of the SAEs resolved, and none were considered related to the study drug. No TEAEs leading to discontinuation occurred during the single-dose period, and 2 subjects discontinued due to TEAEs in the multiple-dose period.

No clinically meaningful trends were noted in laboratory test results, vital signs, or physical examination findings.