Clinical Trial Results Summary
Study EN3202-028

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| **Study Number:** EN3202-028 | |
| **Title of Study:** An Open-Label Effectiveness and Safety Study of Oxymorphone Extended Release in Opioid-Naïve Patients With Chronic Pain | |
| **Investigators:** 29 investigators, 23 of which enrolled patients | |
| **Study Centers:** 29 centers in the United States, 23 of which enrolled patients | |
| **Publication (reference):** None | |
| **Study Period (years):**<br>Date of First Enrollment: June 11, 2003<br>Date of Last Enrollment: January 21, 2004 | **Phase of Development:** Phase III |
| **Objectives:** The primary objective was to evaluate the tolerability of oxymorphone extended release (ER) during dose titration/stabilization. The secondary objectives were to evaluate incidence rates and severity of adverse events (AEs) during the study and to evaluate the maintenance of pain control for an extended period after dose stabilization. | |
| **Methodology:** The study was divided into two study periods:<br>Titration/Stabilization period—Following baseline assessments, patients received 2 days of therapy with oxymorphone ER 5 mg q12h; patients then continued taking 5 mg q12h or titrated to a stabilized dose. Stabilized dose was defined as having an average daily pain score ≤4 on Question 5 of the Brief Pain Inventory (BPI) on 3 of 5 consecutive days while receiving the same total daily dose of study medication. Patients who entered the study with prior stable non-opioid analgesic use could continue their use of these medications while on-study. Immediately upon reaching a stable dose of study medication, the patient entered the Maintenance period. Patients whose dose was not stabilized within 21 days were to be discontinued from the trial. During this period, no changes to concomitant non-opioid analgesics could be made and no rescue medication was available.<br>Maintenance period—Patients whose dose was stabilized entered the Maintenance period and began receiving therapy for up to a total of 6 months after the first 5-mg dose. Patients were permitted to further titrate their dose, and rescue medication (oxymorphone immediate release [IR] 5 mg) was available for breakthrough pain. Any concomitant non-opioid analgesics could be decreased or discontinued; however, no increases in dose or new concomitant non-opioid analgesics could be added.<br>Upon completion of the Maintenance period at the end of Month 6 (or early termination), patients were tapered off of oxymorphone ER over a 1-week period at the discretion of the investigator; however, not all patients tapered, some were switched to another opioid.<br>Patients returned to the study site for study drug dispensing and assessments of accountability, safety, and effectiveness weekly during the Titration/Stabilization period (Weeks 1, 2, and 3) until the patient reached a stable dose of study medication and monthly during the Maintenance period (Months 1, 2, 3, 4, and 5). Patients returned for an end of study visit at Month 6 and a follow-up examination 1 week after the end of study or early termination. Patients also completed daily diaries to record responses to BPI Question 5 (during Titration/Stabilization only), study medication usage (during both periods), and rescue medication usage (during Maintenance only). | |
| **Number of Patients Planned and Analyzed:**<br>Planned: 100<br>Enrolled: 129<br>Treated: 126<br>Analyzed for efficacy and safety: 126 (Treated Patients population) | |

**Diagnosis and Main Criteria for Inclusion:** Males or females, ≥18 years of age, with moderate to severe chronic non-malignant pain of at least 3 months' duration, without prior opioid use (within the past 3 months), currently receiving a stable non-opioid analgesic regimen, with an initial pain intensity score of ≥40 mm on a 100-mm Visual Analogue Scale (VAS) and a categorical pain rating of moderate or severe on a scale of none, mild, moderate, or severe.

**Test Product, Dose and Mode of Administration, Batch Number(s):** EN3202 (oxymorphone ER) 5, 10, and 20 mg tablets administered orally every 12 hours. Patients received 2 days of therapy with oxymorphone ER 5 mg q12h; patients then continued taking 5 mg q12h or titrated to a stabilized dose. Stabilized dose was defined as having an average daily pain score ≤4 on BPI Question 5 on 3 of 5 consecutive days while receiving the same total daily dose of study medication. Lot numbers 313519 for the 5 mg tablets; 310176, 310177, and 310178 for the 10 mg tablets; and 310179 and 310180 for the 20 mg tablets.

**Reference Therapy, Dose and Mode of Administration, Batch Number(s):** None

**Rescue Medication, Dose and Mode of Administration, Batch Number(s):** Oxymorphone hydrochloride IR, 5 mg tablets administered orally as needed as supplemental rescue medication for breakthrough pain. Lot number 313123.

**Duration of Treatment:** 6 months following initial 5 mg dose

**Criteria for Evaluation:**

Effectiveness

Primary—Percentage of patients who discontinued due to AEs during the Titration/Stabilization period

Secondary—

- Average daily pain intensity (BPI Question 5) during the Titration/Stabilization period from patient diary data
- BPI Questions 3, 4, 5, 6, 8, and 9 from visit data
- Average daily dose of oxymorphone ER from patient diary data
- Rescue medication use from patient diary data
- Total daily dose of oxymorphone ER and rescue medication from patient diary data
- Time to stabilization
- Patient and investigator global assessments of pain relief
- Treatment satisfaction from Treatment Satisfaction Questionnaire

Safety

Incidence of AEs, AEs resulting in discontinuation, and serious AEs (SAEs)

**Statistical Methods:**

Efficacy: For BPI, the significance of the mean change from screening was assessed by paired-t-tests. Patients had to have both screening and post-screening values to be included in this analysis. Medians and 95% confidence intervals (95% CIs), for the time to discontinuation due to AEs and time to stabilization, were estimated by using the Kaplan-Meier survival method. Percentage of patients who discontinuation due to AEs, exposure, global assessment results, and treatment satisfaction results were summarized.

Safety: AEs and treatment-related AEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) term and body system and summarized using by descriptive statistics. AEs were summarized by intensity. SAEs and AEs leading to discontinuation were tabulated separately.

**SUMMARY:**

Effectiveness Results:

- During the Titration/Stabilization period, 15.9% (20/126) of treated patients discontinued due to AEs.
- Statistically significant improvements from screening were seen for all BPI Questions at all visits except for BPI Question 5 during the first 2 days of treatment in the Titration/Stabilization period.
- During the Titration/Stabilization period, the average daily dose of oxymorphone ER ranged from an initial mean of 10 mg on Day 1 (n=124) to 59.1 mg on Day 26 (n=16). During the Maintenance period, the average daily dose of oxymorphone ER remained relatively stable through the end of Month 5 (Day 150), ranging from a mean of 27.8 mg for Days 1-30 to 30.8 mg for Days 121-150. From Day 151 to the end of the study, average daily dose decreased to a mean of 22.3 mg.
- During the Maintenance period, 64 of the 94 treated patients took oxymorphone IR as rescue medication. For those patients who took rescue medication, the mean average daily dose of oxymorphone IR ranged from 6.1 mg during Days 31-60 to 7.6 mg during Days 121-150.
- A total of 93 (73.8%) of the 126 treated patients achieved oxymorphone ER dose stabilization, with 51 of these patients achieving stabilization by Day 14 of dosing. The Kaplan-Meier estimate for the median time to stabilization was 16.0 days with a 95% CI estimate of 14.0 to 20.0 days.
- The majority of patients rated their overall pain relief with the study drug as good to excellent. The physicians' global assessment was consistent with patients' assessment. On the Treatment Satisfaction Questionnaire at Month 6/early termination, patients noted a high mean level of satisfaction with oxymorphone compared to their previous pain medication in dosing convenience and in their ability to perform their normal daily activities.

Safety Results:

- Overall 106/126 (84.1%) treated patients reported at least one AE. Most AEs were of mild or moderate intensity according to the investigators. The most frequently reported AEs were constipation, somnolence, nausea, and dizziness in both the Titration/Stabilization and Maintenance periods and nasopharyngitis in the Maintenance period.
- Overall a total of 41 (32.5%) patients discontinued due to AEs. The most frequently-reported AEs leading to discontinuation were nausea, constipation, somnolence, and insomnia.
- Seven (5.6%) patients experienced treatment-emergent SAEs, all except one of which (abdominal pain NOS) were considered by the investigators to be unlikely related to the study drug.
- One patient died of adenocarcinoma of the pancreas 2 months after discontinuing study drug. The event was unlikely related to study drug in the opinion of the investigator.