
Drug Monograph

Generic Name: oxymorphone extended-release

Trade Name: Opana® ER

Dosage Form: 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg Tablets

National Drug Codes (NDC#) 5 mg 63481-812-60, 63481-812-70, 63481-812-20; 7.5 mg 63481-813-60, 63481-813-70, 63481-813-20; 10 mg 63481-814-60, 63481-814-70, 63481-814-20; 15 mg 63481-815-60, 63481-815-70, 63481-815-20; 20 mg 63481-816-60, 63481-816-70, 63481-816-20; 30 mg 63481-817-60, 63481-817-70, 63481-817-20; 40 mg 63481-818-60, 63481-818-70, 63481-818-20

Manufacturer: Endo Pharmaceuticals

ADF Product Classification: None

Executive Summary

Opana® ER (oxymorphone extended-release) is being evaluated by the Drug Formulary Commission for consideration of inclusion on the Massachusetts formulary of therapeutically equivalent substitutions, as outlined in Chapter 258 of the Acts of 2014. This agent is an extended-release (ER) formulation of oxymorphone that is approved by the Food and Drug Administration (FDA) to treat pain in adults severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.^{1,2}

Oxymorphone is a full opioid agonist that is relatively selective for the μ opioid receptor. It can, however, bind to other opioid receptors at higher doses.^{1,2} The FDA approval of this agent was based upon the results of two double-blind (DB), randomized, placebo-controlled trials in patients with moderate to severe chronic low back pain.^{3,4} In addition, there have been several other placebo-controlled or active-controlled trials of the safety and efficacy of Opana® ER (oxymorphone ER) in alleviating moderate to severe pain associated with cancer, osteoarthritis and postoperative pain.⁵⁻⁸ The recommended initial dose of Opana® ER (oxymorphone ER) as the first opioid analgesic is 5 mg every 12 hours. The manufacturer provides a table of conversion factors to calculate initial doses for patients converting from other opioids to Opana® ER (oxymorphone ER) in the prescribing information (Table 5).¹

Opana® ER (oxymorphone ER) and Opana® (oxymorphone) were reintroduced and approved by the FDA in 2006 despite its own advisory committee on pain drugs voting 11 to 2 against it. Previously, this agent had been approved by the FDA in 1959 as an injection, rectal and oral formulation under the brand name of Numorphan® (oxymorphone). The oral form was later removed from the market in 1979 for what was described as commercial reasons by the company. However, there were also many reports of abuse and misuse associated with these agents. Per the 1974 report, "Drugs and Addict Lifestyle," by the National Institute on Drug Abuse, oxymorphone was extremely popular among addicts for its quick and sustained effect.⁹

In February 2012, a reformulated oxymorphone ER formulation became commercially available. This new formulation used INTAC Technology to impart crush-resistant properties. It was thought that this product had adequate physicochemical resistance to crushing and dissolution intended to present obstacle to abuse by non-oral routes of administration (e.g., injecting and snorting). However, postmarket testing showed that although this new version was harder to crush than the previous Opana® ER (oxymorphone ER) formulation, this agent could be compromised by various manipulations such as cutting, grinding or chewing and can be prepared for snorting using commonly available tools and methods. In addition, this product had the potential to be readily prepared for injection, despite the company's claim that the tablets have "resistance to aqueous extraction (e.g., poor syringeability)."¹⁰ There were some reports that a potentially higher percentage of abuse of this agent via injection was taking place with the new reformulation than with the original formulation. The Centers for Disease Control and Prevention state that this reformulation may have been responsible for an outbreak of human immunodeficiency virus (HIV) in individuals in Indiana due to needle sharing from the illicit use of injectable Opana® ER

(oxymorphone ER).¹¹ The FDA , wrote in a formal notice that the abuse potential and warning section of the new formulation's labeling is "virtually identical" to the previous version, and thus did not grant it abuse-deterrent labeling.¹² Similar to all other long-acting opioids, Opana[®] ER (oxymorphone ER) is subject to requirements of the shared system Extended-Release and Long-Acting (ER/LA) Risk Evaluation and Mitigation Strategies (REMS) program.¹³

Reference Data

Oxymorphone is a full opioid agonist that is relatively selective for the μ opioid receptor. It can, however, bind to other opioid receptors at higher doses. Although the precise mechanism of action is unknown, specific central nervous system (CNS) opioid receptors for endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.^{1,2} In addition to the analgesic effect, the binding of Opana® ER (oxymorphone ER) to μ receptors produces a variety of other potential unwanted side effects including bradycardia, sedation, euphoria, physical dependence, and potentially respiratory depression.^{1,2}

Opana® ER (oxymorphone ER), is estimated to be three times as potent as oral morphine and twice as potent as oral oxycodone when calculating equianalgesic doses using available opioid calculators (e.g., <http://www.healthquality.va.gov/guidelines/Pain/cot/OpioidTherapyPocketCardFinalpress.pdf>). This agent joins multiple other long-acting opioids available on the market, some of which also have abuse-deterrent properties.² A list of these medications is shown below in Table 1.

Table 1. Long-Acting Opioid Availability¹⁴

Generic Name (Trade name)	Abuse Deterrent Formulation Available	Commercially Available
Buprenorphine (Belbuca®, Butrans®)	-	✓
Fentanyl (Duragesic®)	-	✓
Hydrocodone (Hysingla ER®)	✓	✓
Hydrocodone (Zohydro ER®)	-	✓
Hydromorphone (Exalgo®)	-	✓
Levorphanol (Levo-Dromoran®)	-	✓
Methadone (Diskets Dispersible®, Dolophine®, Methadose®, Methadone Intensol®)	-	✓
Morphine sulfate (Avinza®, Kadian®, MS Contin®)	-	✓
Morphine sulfate (Morphabond®)	✓	-
Morphine sulfate/naltrexone (Embeda®)	✓	✓
Oxycodone (OxyContin®)	✓	✓
Oxycodone (Xtampza ER®)	✓	-
Oxycodone/naloxone (Targiniq ER®)	✓	-
Oxymorphone (Opana® ER)	-	✓
Tapentadol (Nucynta ER®)	-	✓

*Xtampza ER® approval is tentative, pending patent litigation

Therapeutic Indications/Efficacy

Opana® ER (oxymorphone ER) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults. This ER formulation is not indicated as an as-needed analgesic.^{1,2}

The available safety and efficacy studies for Opana® ER (oxymorphone ER) are outlined in Table 2. In clinical studies, oxymorphone has demonstrated superior analgesic efficacy versus placebo and comparable analgesic efficacy versus oxycodone controlled-release (CR) and morphine CR. The first three trials outlined for the management of low back pain were all DB, placebo-controlled, randomized controlled trials.^{3,4,15}

The first included a four week open-label phase in which individuals were titrated with Opana® ER (oxymorphone ER) in 5 to 10 mg increments every 12 hours, every three to seven days until they achieved a well-tolerated, stable dose. From this population, 205 individuals were then randomized in a DB, 12 week-phase of either Opana® ER (oxymorphone ER) or placebo. The primary endpoint of pain intensity from baseline to final study visit was evaluated. For patients completing titration, average pain intensity for the Opana® ER (oxymorphone ER) group decreased from 69.4 mm to 22.7 mm ($P<0.0001$). In addition, pain intensity was found to increase significantly more in the placebo group (least squares [LS] mean change 26.9 \pm 2.4 [median 28.0]) than in the Opana® ER (oxymorphone ER) group (LS mean change 10.0 \pm 2.4 [median 2.0]; $P<0.0001$).³

After randomization, sixty-eight percent of patients treated with Opana® ER (oxymorphone ER) completed the 12-week treatment compared to 47% of patients treated with placebo. Approximately 8% of patients in each group discontinued due to adverse events. Opioid withdrawal was noted to occur in two patients in the placebo group and one in the Opana® ER (oxymorphone ER) group.³

The second trial also included an open-label phase in which a total of 143 individuals were successfully titrated to a stable dose of Opana® ER (oxymorphone ER) and were then entered into a 12-week, DB treatment phase of Opana® ER (oxymorphone ER) or placebo every 12 hours (Q12H). The primary endpoint of pain intensity increased significantly more for those randomized to placebo than for those who continued their stabilized dose of Opana® ER (oxymorphone ER). The increase from baseline to final visit was 31.6 mm for placebo compared to 8.7 mm with Opana® ER (oxymorphone ER) ($P<0.0001$).⁴

Additional endpoints evaluated included the time to discontinuation due to lack of efficacy which occurred in 53% of placebo patients compared to 11% of Opana® ER (oxymorphone ER) patients ($P<0.001$). Discontinuations due to an adverse event were found to be similar for both groups: 10% with placebo and 11% with Opana® ER (oxymorphone ER). The most commonly reported adverse events were nausea, constipation, headache and somnolence. Opioid withdrawal was noted to occur in five patients in the placebo group and none in the Opana® ER (oxymorphone ER).⁴

The third trial included a two week titration period during which 213 individuals were randomized to Opana® ER (oxymorphone ER) or OxyContin® (oxycodone CR) Q12H. Those stabilized on a dosage during this period were then entered into an 18-day DB phase in which they either continued their stabilized opioid or were switched to placebo Q12H. For the primary endpoint of pain intensity, the mean change in pain intensity (VAS) from baseline to study end point was significantly greater for placebo than for oxymorphone ER or oxycodone CR, with comparable changes in the two active treatment groups. For oxymorphone ER and oxycodone CR the LS mean differences with placebo were -18.21 (95% CI, -25.83 to -10.58; $P=0.0001$) and -18.55 (95% CI, -26.1 to -10.98; $P=0.0001$), respectively.¹⁵

Other recorded end points included categorical pain ratings which were found to be significantly lower in patients receiving Opana® ER (oxymorphone ER) compared to placebo ($P=0.0001$). Similar results were obtained for the OxyContin® (oxycodone CR) group. Both active agents maintained pain relief scores, with 61% of patients receiving either Opana® ER (oxymorphone ER) or OxyContin® (oxycodone CR) reporting moderate to complete pain relief compared to 28% for placebo ($P=0.0006$ and $P=0.0001$, respectively). For the time to treatment failure, 57% of patients receiving placebo discontinued therapy due to lack of efficacy, compared with 20% for the Opana® ER (oxymorphone ER) group and 16% for the OxyContin® (oxycodone CR) group ($P=0.0001$ for both drugs). Lastly, in the first four days of the DB treatment phase, when the use of rescue medication was unrestricted, the mean daily dosage of rescue medication was less for patients receiving Opana® ER (oxymorphone ER) (25.5 mg; $P=0.0068$) or OxyContin® (oxycodone CR) (24.4 mg; $P=0.0024$) than for those receiving placebo (34.8 mg).¹⁵

The safety and effectiveness of Opana® ER (oxymorphone ER) has also been evaluated in adult patients with cancer pain requiring opioid therapy. In one pilot study, 86 individuals were first stabilized for ≥ 3 days on morphine CR or oxycodone CR and then entered into the first 7-day treatment period (period 1).

From this initial group, 63 patients who completed stabilization were then successfully crossed over to Opana® ER (oxymorphone ER) at an estimated equianalgesic dosage and treated for an additional seven days (period 2).⁵

Mean daily pain intensity scores were comparable for all agents during each treatment sequence, indicating that pain was stabilized throughout the study. When averaged over the last two days (days six and seven) of each treatment period, a similar level of pain relief was achieved with Opana® ER (oxymorphone ER) as with oxycodone CR or morphine CR. There were no significant differences in daily pain intensity scores between Opana® ER (oxymorphone ER) and either morphine CR or oxycodone CR. The tolerability and safety profiles were similar for all agents.⁵

The second study that evaluated Opana® ER (oxymorphone ER) in cancer patients was a post-hoc analysis of two, one-year, open-label, and extension studies (ES). Patients who had been taking Opana® ER (oxymorphone ER) continued the stabilized dose from the previous study; patients who had been taking a comparator opioid were switched to an equianalgesic dose of Opana® ER (oxymorphone ER). Of the 80 patients who were entered into the ES, 26 patients completed all 52 weeks. Seven of the patients who discontinued stated it was due to a loss of effectiveness with the agent provided and 20 patients discontinued owing to adverse events (most unrelated to the study drug).⁶

No significant increase in mean pain intensity was observed from baseline (30.5 [19.6], 100-point scale) to final visit (35.9 [21.1]; $P=0.37$). The most common adverse events were concomitant disease progression (28.8%; $n=23$), nausea (22.5%; $n=18$), dyspnea (16.3%; $n=13$), fatigue (16.3%; $n=13$) and edema of the lower limb (15%; $n=12$).⁶

Finally, this agent has been evaluated in a DB, randomized, placebo-controlled trial in patients 18 years of age and older with osteoarthritis who were regularly taking acetaminophen, non-steroidal-antiinflammatory drugs or opioids for 90 days prior to the screening visit with suboptimal analgesic response. This study compared the analgesic effect of three doses of Opana® ER (oxymorphone ER) Q12H with those of placebo. After a washout period of two to seven days, 370 individuals were randomized to receive one of the four treatment regimens for a period of two weeks. The primary endpoint of mean change in arthritis pain intensity was evaluated.⁷

From the 198 individuals who completed the study, the LS mean change in arthritis pain intensity from baseline to the final visit, as measured on the 100-mm VAS, were -21, -28, -29 and -17 mm for Opana® ER (oxymorphone ER) 10, 40 and 50 mg; and placebo, respectively ($P=0.002$). Compared to placebo, arthritis pain intensity scores were improved by 62.8% and 70.9% after treatment with Opana® ER (oxymorphone ER) 40 or 50 mg Q12H, respectively ($P=0.012$ and $P=0.006$). All patients who received Opana® ER (oxymorphone ER), irrespective of the dose, had significant improvements in the Short-Form Health Survey (SF-36) quality of life score compared to placebo. The changes from baseline were 3.9, 4.6, 3.6 and -0.1 points with Opana® ER (oxymorphone ER) 10, 40 and 50 mg; and placebo, respectively ($P<0.001$). Improvements in the Chronic Pain Sleep Inventory (CPSI) scores for overall sleep quality were two-fold greater in patients who received Opana® ER (oxymorphone ER) 40 and 50 mg than in the placebo group ($P\leq 0.05$). The majority of adverse events reported with Opana® ER (oxymorphone ER) were noted to be mild to moderate in intensity. However, three serious adverse events (urinary retention, central nervous depression and pancreatitis) were possibly related to this agent.⁷

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Low Back Pain				
<p>Katz et al³ (abstract)</p> <p>OL phase of four weeks: Opana[®] ER (oxymorphone ER) (5 mg Q12H for two days then patients were titrated in 5 to 10 mg increments every three to seven days until a well-tolerated, stable dose was determined</p> <p>After four weeks, patients that were stabilized during OL period were randomized into 12-week DB phase:</p> <p>Opana[®] ER (oxymorphone ER) individualized stable dose Q12H</p> <p>vs</p>	<p>DB, PC, PG, RCT</p> <p>Patients ≥18 years of age with chronic low back pain suboptimally responsive to nonopioid therapy</p>	<p>N=325</p> <p>12 weeks (DB treatment period)</p>	<p>Primary:</p> <p>Pain intensity: Change in average pain intensity (VAS) from baseline (before randomization) to final study visit (at the end of double-blind treatment or at early discontinuation)</p> <p>Secondary:</p> <p>Not reported</p>	<p>Primary:</p> <p>Sixty-three percent of patients (205/325) were successfully titrated to a stable dose of Opana[®] ER (oxymorphone ER) during the open-label titration period. From this group, the mean ± SD VAS score at screening was 69.4 ± 11.8 mm and at baseline (beginning of double-blind period) the scores were 18.5 ± 11.2 mm and 19.3 ± 11.3 mm for the Opana[®] ER (oxymorphone ER) and placebo groups, respectively. For patients completing titration, average pain intensity for the Opana[®] ER (oxymorphone ER) group decreased from 69.4 mm to 22.7 mm (P<0.0001). In addition, pain intensity was found to increase significantly more in the placebo group (least squares [LS] mean change 26.9+/- 2.4 [median 28.0]) than in the Opana[®] ER (oxymorphone ER) group (LS mean change 10.0 +/- 2.4 [median 2.0]; P<0.0001).</p> <p>After randomization, sixty-eight percent of patients treated with Opana[®] ER (oxymorphone ER) completed the 12-week treatment compared to 47% of patients treated with placebo. Approximately 8% of patients in each group discontinued due to adverse events. Significantly more patients in the placebo group discontinued treatment due to lack of efficacy than the oxymorphone ER group (P<0.0001). Opioid withdrawal was noted to occur in two patients in the placebo group and one in the Opana[®] ER (oxymorphone ER) group.</p> <p>Secondary:</p> <p>Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>During first four days of DB treatment, patients were allowed an unlimited number of Opana® (oxymorphone IR) 5 mg tablets every four to six hours as needed; thereafter, the number was limited to two tablets per day.</p>				
<p>Hale et al⁴</p> <p>Prior to entering OL phase, individuals were titrated from current opioid to equianalgesic dose of Opana® ER (oxymorphone ER) Q12H</p> <p>OL phase: Individuals were stabilized on dose of Opana® ER (oxymorphone ER) Q12H that reduced average pain to <40 mm on</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥18 years of age with moderate to severe chronic low back pain that had been present for at least several hours a day for a minimum of three months; receiving stable ATC opioid pain medication equivalent to at least 60 mg per day of oral morphine for the two weeks prior to screening</p>	<p>N=250</p> <p>12 Weeks (DB treatment phase)</p>	<p>Primary: Change in average pain intensity (VAS) from baseline (before randomization) to final study visit (at the end of double-blind treatment or at early discontinuation)</p> <p>Secondary: Time to discontinuation caused by lack of efficacy</p>	<p>Primary: Fifty-six percent of patients (143/250) were successfully titrated to a stable dose of Opana® ER (oxymorphone ER) during the open-label titration period.</p> <p>Pain intensity was shown to have increased significantly more for those randomized to placebo than for those who continued their stabilized dose of Opana® ER (oxymorphone ER). The increase from baseline to final visit was 31.6 mm for placebo compared to 8.7 mm with Opana® ER (oxymorphone ER) (P<0.0001).</p> <p>Secondary: After randomization, 70% of patients in the Opana® ER (oxymorphone ER) group and 25% of patients in the placebo group completed the 12-week double-blind treatment. Fifty-three percent of placebo patients compared to 11% of Opana® ER (oxymorphone ER) patients discontinued due to lack of efficacy (P<0.001).</p> <p>Discontinuations due to an adverse event were found to be similar for both groups: 10% with placebo and 11% with Opana® ER</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>a VAS scale with good tolerability (titrated by 10 mg increments every three to seven days if needed)</p> <p>Once stabilized, individuals randomized 1:1 for 12-weeks DB-Phase:</p> <p>Opana® ER (oxymorphone ER) individualized stable dose Q12H</p> <p>vs</p> <p>placebo</p> <p>During first four days of DB treatment, patients were allowed an unlimited number of Opana® (oxymorphone IR) 5 mg tablets every four to six hours as needed; thereafter, the number was limited to two tablets per day.</p>				<p>(oxymorphone ER). The most commonly reported adverse events were nausea, constipation, headache and somnolence. Opioid withdrawal was noted to occur in five patients in the placebo group and none in the Opana® ER (oxymorphone ER).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Hale et al¹⁵</p> <p>Titration phase (seven to 14 days): Oxymorphone ER (10 to 110 mg) Q12H</p> <p>vs</p> <p>oxycodone CR (20 to 220 mg) Q12H</p> <p>then, individuals entered 18-day DB treatment phase:</p> <p>stabilized opioid therapy (either oxymorphone ER or oxycodone CR) Q12H</p> <p>vs</p> <p>placebo Q12H</p>	<p>AC, DB, MC, PC, RCT</p> <p>Patients 18 to 75 years of age with moderate to severe chronic low back pain requiring stable opioid therapy for at least three consecutive days before screening</p>	<p>N=213</p> <p>18 days (DB treatment period)</p>	<p>Primary: Change in pain intensity from baseline to study end point as assessed by a 100-mm VAS measured four hours after morning dose</p> <p>Secondary: Pain intensity assessed by a categorical scale, pain relief, BPI, patient, global assessments, time to treatment failure, and use of rescue medications</p>	<p>Primary: During the DB treatment phase, the mean change in pain intensity (VAS) from baseline to study end point was significantly greater for placebo than for oxymorphone ER or oxycodone CR, with comparable changes in the two active treatment groups. For oxymorphone ER and oxycodone CR the LS mean differences with placebo were -18.21 (95% CI, -25.83 to -10.58; P=0.0001) and -18.55 (95% CI, -26.1 to -10.98; P=0.0001), respectively.</p> <p>Secondary: Categorical pain ratings were significantly lower in patients receiving oxymorphone ER compared to placebo (P=0.0001). Similar results were obtained for the oxycodone CR group.</p> <p>In contrast to placebo, both agents maintained pain relief scores, with 61% of patients receiving oxymorphone ER or oxycodone CR reporting moderate to complete pain relief compared to 28% for placebo (P=0.0006 and 0.0001, respectively).</p> <p>At the study end point, significantly more patients who received oxymorphone ER (59%) and oxycodone CR (63%) rated their medication as “good”, “very good,” or “excellent” compared with placebo (27%; P=0.0001 for each agent).</p> <p>For the time to treatment failure, 57% of patients receiving placebo discontinued therapy due to lack of efficacy, compare with 20% for the oxymorphone ER group and 16% for the oxycodone CR group (P=0.0001 for both drugs).</p> <p>In the first four days of the double-blind treatment phase, when the use of rescue medication was unrestricted, the mean daily dosage of rescue medication was significantly less for patients receiving oxymorphone ER (25.5 mg; P=0.0068) or oxycodone CR (24.4 mg; P=0.0024) than for those receiving placebo (34.8 mg).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse events for the active drugs were similar; the most frequent were constipation and sedation.
Cancer Pain				
<p>Sloan et al⁵</p> <p>Oxymorphone ER</p> <p>Patients were stabilized for ≥3 days on morphine CR (MS Contin®) or oxycodone CR (OxyContin®) [drug selection based upon patients' previous use or investigator preference], and then treated for seven days at their stabilized dose of respective medication (Period 1)</p> <p>Patients were then crossed over for seven days of treatment at an estimated equianalgesic dosage of oxymorphone ER (Period 2)</p>	<p>MC, MD, OL, PRO, XO</p> <p>Patients 18 to 80 years of age with a history of chronic cancer pain requiring ≥20 mg of oxycodone or the analgesic equivalent of ≥30 mg of oral morphine per day</p>	<p>N=63</p> <p>7 days (Period 2)</p>	<p>Primary: Pain intensity</p> <p>Secondary: Equianalgesic dose ratios, quality of life assessments, safety</p>	<p>Primary: A total of 63/86 patients completed stabilization in Period 1 and then went on to begin treatment with oxymorphone ER. From this group, 93.7% (59/63) completed treatment with oxymorphone ER.</p> <p>Mean daily pain intensity scores were comparable for all agents during each treatment sequence, indicating that pain was stabilized throughout the study. When averaged over the last two days (days six and seven) of each treatment period, a similar level of pain relief was achieved with oxymorphone ER as with oxycodone CR or morphine CR.</p> <p>Secondary: The average scheduled daily dose of study medication and the average total daily dose decreased after crossover to oxymorphone ER.</p> <p>There were no significant changes in the mean VAS scores for quality of life domains or for the mean change in patient recall for the quality of sleep for oxymorphone ER compared with morphine CR or oxycodone CR.</p> <p>The tolerability and safety profiles were similar for all agents.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oral IR formulation of study medication (morphine, oxycodone or oxymorphone) were available as a rescue medication (approximately 10% of the total daily dose of scheduled ER medication) during periods 1 and 2				
<p>Slatkin et al⁶ (abstract)</p> <p>Oxymorphone ER</p> <p>Patients who had been taking oxymorphone ER continued the dose established in a previous study; patients who had been taking a comparator opioid were switched to an equianalgesic dose of oxymorphone ER</p>	<p>Post-hoc analysis of two ES, OL studies</p> <p>Patients with cancer who had participated in two short-term crossover comparator trial of oxymorphone ER</p>	<p>N=80</p> <p>12 months</p>	<p>Primary:</p> <p>Current, average, worst and least pain scores normalized to a 100-point scale</p> <p>Secondary:</p> <p>Patients rated global assessment of study medication and adverse events</p>	<p>Primary:</p> <p>Of the 80 patients who were entered into the ES, 26 patients completed 52 weeks, seven patients discontinued due to a stated loss of effectiveness, and 20 patients discontinued owing to adverse events (most unrelated to the study drug).</p> <p>No significant increase in mean SD average pain intensity was observed from baseline (30.5 [19.6], 100-point scale) to final visit (35.9 [21.1]; P=0.37).</p> <p>Secondary:</p> <p>The most common adverse events were concomitant disease progression (28.8%; n=23), nausea (22.5%; n=18), dyspnea (16.3%; n=13), fatigue (16.3%; n=13) and edema of the lower limb (15%; n=12).</p> <p>Patient rated global assessment of study medication was not reported in the abstract.</p>
Osteoarthritis Pain				
Kivitz et al ⁷	DB, DR, MC, PC,	N=370	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Oxymorphone ER 10 mg Q12H for two weeks</p> <p>vs</p> <p>oxymorphone ER 20 mg Q12H for one week, followed by oxymorphone ER 40 mg Q12H for one week</p> <p>vs</p> <p>oxymorphone ER 20 mg Q12H for one week, followed by oxymorphone ER 50 mg Q12H for one week</p> <p>vs</p> <p>placebo</p>	<p>RCT</p> <p>Patients ≥ 18 years of age with OA (defined by the presence of typical knee or hip joint symptoms [pain, stiffness, and disability] and signs [bony crepitus], and radiographic evidence of OA [grade II-IV in the index joint on the Kellgren-Lawrence scale]); who are regularly taking acetaminophen, NSAIDs or opioid analgesics for 90 days before the screening visit with suboptimal analgesic response</p>	<p>2 weeks</p>	<p>Mean change in arthritis pain intensity</p> <p>Secondary: Change in pain, stiffness, and physical function subscales of WOMAC OA index and WOMAC composite index; SF-36 quality of life, CPSI and tolerability</p>	<p>In the ITT population, the LS mean change in arthritis pain intensity from baseline to the final visit, as measured on the 100-mm VAS, were -21, -28, -29 and -17 mm for oxymorphone ER 10, 40 and 50 mg; and placebo, respectively (P=0.002). The LS mean differences in change from baseline compared to placebo were -4.3 (95% CI, -12.8 to -4.3; P value not significant), -11.1 (95% CI, -19.7 to -2.5; P=0.012) and -12.2 (95% CI, -20.9 to -3.5; P=0.006) for the oxymorphone ER 10, 40 and 50 mg doses, respectively. Compared to placebo, arthritis pain intensity scores were improved by 62.8% and 70.9% after treatment with oxymorphone ER 40 or 50 mg Q12H, respectively (P=0.012 and P=0.006).</p> <p>Secondary: Overall, improvements in WOMAC scores were two- to three-fold greater in oxymorphone ER groups compared to placebo. From baseline to the final visit, two-fold greater decreases in WOMAC pain subscale scores were found in all three oxymorphone ER groups compared to the placebo group (P≤0.025). Improvements in WOMAC physical function subscale scores also were significantly greater for each of the oxymorphone ER groups compared to the placebo group (P≤0.025). Improvements in the WOMAC stiffness subscale score were significant compared to placebo only for the oxymorphone ER 40 and 50 mg groups (P≤0.001). With respect to the WOMAC composite index, pairwise comparisons of the placebo group with each of the oxymorphone groups found significantly greater improvements in each oxymorphone ER group (P≤0.025).</p> <p>All patients who received oxymorphone ER, irrespective of the dose, had significant improvements in the SF-36 quality of life score compared to placebo. The changes from baseline were 3.9, 4.6, 3.6 and -0.1 points with oxymorphone ER 10, 40 and 50 mg; and placebo, respectively (P<0.001).</p> <p>Improvements in the CPSI scores for overall sleep quality were two-fold greater in patients who received oxymorphone ER 40 and 50 mg</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>than in the placebo group ($P \leq 0.05$).</p> <p>The most frequently reported adverse event in the oxymorphone ER groups were nausea (39.4%), vomiting (23.7%), dizziness (22.6%), constipation (22.2%), somnolence (17.6%), pruritus (16.5%) and headache (14.7%).</p>

Drug regimen abbreviation: Q12H=every 12 hours

Study abbreviations: AC=active-controlled, ATC=around-the-clock, BPI=Brief Pain Inventory, CI=confidence interval, CPSI=Chronic Pain Sleep Inventory, CR=controlled-release, DB=double-blind, DR=dose-ranging, ER=extended-release, ES=extension study, IR=immediate-release, ITT=intent-to-treat, MC=multicenter, MD=multi-dose, NSAIDS=non-steroidal antiinflammatory drugs, OA=osteoarthritis, OL=open-label, PC=placebo-controlled, PCA= patient controlled analgesia, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SD=standard deviation, SF-36=short form 36 health assessment questionnaire, TEAE=treatment-emergent adverse event, VAS=visual analog scale, WOMAC index=Western Ontario and McMaster Universities Index

Pharmacokinetics/Pharmacogenomics

Absorption

The oral bioavailability of oxymorphone is approximately 10%. The range of mean (\pm SD) elimination half-lives ($t_{1/2}$) after single doses of all strengths of Opana® ER (oxymorphone ER) is from 9.35 hours (\pm 2.94) to 11.30 hours (\pm 10.81). Peak plasma levels (C_{max}) and extent of absorption (AUC) are proportional with dose for single-dose and steady-state conditions. The time to peak plasma concentration (T_{max}) for Opana® ER (oxymorphone ER) was observed to be 1 hour with a C_{max} of 2.8 ng/mL in fasted subjects compared to a T_{max} of 2 hours with a C_{max} of 4.25 ng/mL in fed subjects after single doses of a 40 mg tablet. Due to these observations, the manufacturer recommends dosing at least one hour prior to a meal or two hours after a meal.¹ The T_{max} for Opana® ER (oxymorphone ER) tablets that have been crushed or otherwise tampered with has not been published.

Distribution

Oxymorphone is not extensively bound to human plasma proteins; binding is in the range of 10% to 12%.^{1,2}

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites. The two major metabolites of oxymorphone are oxymorphone-3-glucuronide and 6-OH-oxymorphone. The mean plasma area under the curve (AUC) for oxymorphone-3-glucuronide is approximately 90-fold higher than the parent compound. The pharmacologic activity of the glucuronide metabolite has not been evaluated. 6-OH-oxymorphone has been shown in animal studies to have analgesic bioactivity. The mean plasma 6-OH-oxymorphone AUC is approximately 70% of the oxymorphone AUC following single oral doses, but is essentially equivalent to the parent compound at steady-state.^{1,2}

Excretion

Because oxymorphone is extensively metabolized, <1% of the administered dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and less than 1% excreted as 6-OH-oxymorphone in subjects with normal hepatic and renal function.^{1,2}

There are no pharmacogenomics data reported for Opana® ER (oxymorphone ER).

Special Populations

Table 3. Special Populations¹

Population	Precaution
Elderly	<p>Among the total number of individuals in clinical trials, only a small number were elderly, including 27% over the age of 65 years and 9% over the age of 75. No overall differences in effectiveness were observed between the elderly and younger individuals; however, some adverse events were more common in those over 65 years compared to younger individuals.</p> <p>The steady-state plasma concentrations of oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide are approximately 40% higher in elderly subjects (\geq 65 years) than in young subjects (18 to 40 years). On average, age > 65 years was associated with a 1.4-fold increase in oxymorphone AUC and a 1.5-fold increase in C_{max}, which was not observed to be related to a difference in body weight, metabolism, or excretion of oxymorphone.</p> <p>For patients \geq 65 years of age, it is recommended to initiate dosing at 5 mg. For those individuals on prior opioid therapy, start the Opana® ER (oxymorphone ER) at 50%</p>

	lower than the starting dose for a younger patient on prior opioids and titrate slowly.
Renal dysfunction	<p>Moderate to severe renal impairment may result in an increase in oxymorphone bioavailability ranging from 57 to 65%. In a pharmacokinetic study involving 24 patients with renal dysfunction compared to healthy patients, there was an increase of 26%, 57%, and 65% in oxymorphone bioavailability in mild (CrCl: 51 to 80 mL/min; n=8), moderate (CrCl: 30 to 50 mL/min; n=8), and severe (CrCl: < 30 mL/min; n=8), respectively.</p> <p>In patients with CrCl rates less than 50 mL/min, start dosing at 5 mg in the opioid-naïve patient. For patients on prior opioid therapy, start Opana[®] ER (oxymorphone ER) at 50% lower than the starting dose for a patient with normal renal function on prior opioids and titrate slowly.</p>
Hepatic dysfunction	<p>Patients with mild hepatic impairment have an increase in oxymorphone bioavailability of 1.6-fold and 3.7-fold in patients with moderate hepatic impairment. For one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold.</p> <p>In opioid-naïve patients with mild hepatic impairment, initiate therapy using the 5 mg dose and monitor closely. For opioid-experienced patients, start at 50% lower than the starting dose for a patient with normal hepatic function on prior opioids and titrate slowly. Do not use in patients with moderate and severe hepatic impairment.</p>
Pregnancy/nursing	<p>Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Opioids cross the placenta and may produce respiratory depression in neonates; therefore, it is not for use in women during and immediately prior to labor.</p> <p>It is not known if oxymorphone is excreted in breast milk. Since some opioids are excreted in human milk, use caution when oxymorphone is administered to a nursing woman and monitor the infant closely.</p>
Children	The safety and efficacy in individuals less than 18 years of age have not been established.*
Gender/Race	<p>After single- and multiple-doses of oxymorphone ER, female subjects tended to have a slightly higher AUC at steady state and C_{max} values than male subjects; however, gender differences were not observed when AUC at steady state and C_{max} values were adjusted by body weight.</p> <p>No race-specific differences in pharmacokinetic data have been identified.</p>

*No adequate or well-controlled trials.

CrCl=creatinine clearance

In vitro studies resulted in little-to-no biotransformation of oxymorphone to 6-OH-oxymorphone by any of the major CYP450 isoforms at therapeutically relevant oxymorphone plasma concentrations. Clinical drug interaction studies with oxymorphone hydrochloride ER tablets found no induction of CYP 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required.

Dosage Forms

Table 4. Availability, Storage and Handling¹

Dosage Form	Strength	Special Handling or Storage
Extended-release tablet	5 mg	Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F).
	7.5 mg	
	10 mg	
	15 mg	Dispense in a tight container as defined in

Dosage Form	Strength	Special Handling or Storage
	20 mg 30 mg 40 mg	the United States Pharmacopeia (USP), with a child-resistant closure (as required).

Dosage Range¹⁻²

Please be aware that oxymorphone is available as both immediate-release 5 and 10mg tablets and extended-release 5 and 10 mg tablets.

Initial dosing:

The dosing regimen for each patient should be individualized, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse and misuse.

Use of Opana[®] ER (oxymorphone ER) as the first opioid analgesic or in patients who are not opioid tolerant:

Opana[®] ER (oxymorphone ER) 5 mg orally every 12 hours

Adult patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 µg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from Opana[®] (oxymorphone) to Opana[®] ER (oxymorphone ER):

Patients receiving Opana[®] (oxymorphone) may be converted to Opana[®] ER (oxymorphone ER) by administering half the patient's total daily oral Opana[®] (oxymorphone) dose as Opana[®] ER (oxymorphone ER), every 12 hours.

Conversion from parenteral oxymorphone to Opana[®] ER (oxymorphone ER):

Convert patients receiving parenteral oxymorphone to Opana[®] ER (oxymorphone ER) by administering ten times the patient's total daily parenteral oxymorphone dose as Opana[®] ER (oxymorphone ER) in two equally divided doses (e.g., [IV dose x 10] divided by 2). Due to patient variability, monitor patients closely upon conversion to evaluate for adequate analgesia and side effects.

Conversion from other oral opioids to Opana[®] ER (oxymorphone ER):

Discontinue all other around-the-clock opioid drugs when Opana[®] ER (oxymorphone ER) therapy is initiated.

While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioids. It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone requirements which could result in adverse reactions.

In one open-label clinical trial of Opana[®] ER (oxymorphone ER), the following table (Table 5) was utilized as a guide for titration to Opana[®] ER (oxymorphone ER). The conversions in this table are only for the conversion from one of the listed oral opioids to Opana[®] ER (oxymorphone ER).

Table 5. Conversion Factors to Opana[®] ER (oxymorphone ER)

Conversion factors	
Prior oral opioid	Approximate oral conversion factor
Oxymorphone	1
Hydrocodone	0.5
Oxycodone	0.5

Methadone	0.5
Morphine	0.333

For patients on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the conversion factor to calculate the approximate oral oxymorphone daily dose.

For patients on a regimen of more than one opioid, calculate the approximate oral oxymorphone dose for each opioid and sum the totals to obtain the approximate total oxymorphone daily dose.

For patients on a regimen of fixed-ratio opioid/nonopioid analgesic products, use the opioid component of these products in the conversion. The dose should always be rounded down, if necessary, to the appropriate Opana® ER (oxymorphone ER) strength(s) available.

Conversion from methadone to Opana® ER (oxymorphone ER):

It is important to perform close monitoring of the patient when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Titration and maintenance of therapy:

Individually titrate Opana® ER (oxymorphone ER) to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Opana® ER (oxymorphone ER) to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, and misuse. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the Opana® ER (oxymorphone ER) dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within three days, dosage adjustments, preferably at increments of 5 to 10 mg every 12 hours, may be done every three to seven days.

Patients who experience breakthrough pain may require a dose increase of Opana® ER (oxymorphone ER), or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Hepatic Insufficiency

Opana® ER (oxymorphone ER) is contraindicated in patients with moderate to severe hepatic impairment. In opioid-naïve patients with mild hepatic impairment, initiate treatment with the 5 mg dose. For patients on prior opioid therapy, start Opana® ER (oxymorphone ER) at 50% lower than the starting dose for a patient with normal hepatic function on prior opioids and titrate slowly. Monitor patients closely for signs of respiratory or central nervous system depression.

Renal Insufficiency

In patients with creatinine clearance rates less than 50 mL/min, start Opana® ER (oxymorphone ER) in the opioid-naïve patient with the 5 mg dose. For patients on prior opioid therapy, start Opana® ER (oxymorphone ER) at 50% lower than the starting dose for a patient with normal renal function on prior opioids and titrate slowly. Monitor patients closely for signs of respiratory or central nervous system depression.

Geriatric Patients

The steady-state plasma concentrations of oxymorphone are approximately 40% higher in elderly subjects than in young subjects. Initiate dosing with Opana® ER (oxymorphone ER) in patients 65 years of age and over using the 5 mg dose and monitor closely for signs of respiratory and central nervous system depression when initiating and titrating Opana® ER (oxymorphone ER) to adequate analgesia. For patients on prior opioid therapy, start Opana® ER (oxymorphone ER) at 50% lower than the starting dose for a younger patient on prior opioids and titrate slowly.

Special considerations

Administration requirements

Opana® ER (oxymorphone ER) tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Administer on an empty stomach, at least one hour prior to or two hours after eating.

In general, Opana® ER (oxymorphone ER) should be taken at 12-hour intervals.

Discontinuation of Opana® ER (oxymorphone ER):

When the patient no longer requires therapy with Opana® ER (oxymorphone ER), gradually titrate the dosage downward to prevent signs and symptoms of withdrawal in the physically dependent patient. Do not abruptly discontinue Opana® ER (oxymorphone ER).

Precautions

Table 6. Warnings/Precautions^{1,2}

Warnings/ Precautions	<p>Addiction, abuse and misuse; Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Opana® ER (oxymorphone ER). Addiction can occur at recommended doses in addition to if the drug is purposefully misused or abused. Assess each patient's risk for opioid addiction, abuse or misuse prior to prescribing this agent, and monitor all patients receiving this agent for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse or mental illness. The potential for these risks should not, however, prevent the proper management of pain in any given patient. Abuse, or misuse of this agent by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxymorphone and can result in overdose and death. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug.</p> <p>Life threatening respiratory depression; Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Life-threatening or fatal respiratory depression can occur at any time during the use of this medication. However, the risk is generally greatest during the initiation of therapy or following a dose increase. Individuals should be closely monitored for respiratory depression when initiating therapy and following dose increases.</p> <p>Neonatal opioid withdrawal syndrome; Prolonged use during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be</p>
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	<p>available.</p> <p>Interactions with central nervous system depressants; Hypotension, profound sedation, coma, respiratory depression, or death may result if Opana[®] ER (oxymorphone ER) is used concomitantly with other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids, etc.). In addition, the patient's use of alcohol or illicit drugs that can cause CNS depression should be evaluated. If the decision is made to begin therapy with this agent, the starting dose should be 5 mg every 12 hours with frequent monitoring. Consideration should also be given to using a lower dose of the concomitant CNS depressant.</p> <p>Elderly, cachectic and debilitated patients; Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Patients should be monitored closely when initiating or titrating Opana[®] ER (oxymorphone ER) as well as when this agent is given concomitantly with CNS depressants.</p> <p>Chronic pulmonary disease; Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression. Even at usual therapeutic doses, these agents may decrease respiratory drive to the point of apnea. Consideration should be given to the use of alternative nonopioid analgesics in these patients if possible.</p> <p>Hypotensive effects; Opana[®] ER (oxymorphone ER) may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Avoid use in patients with circulatory shock.</p> <p>Head injury or increased intracranial pressure; Monitor patients taking Opana[®] ER (oxymorphone ER) who may be susceptible to the intracranial effects of carbon dioxide (CO₂) retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy. Opana[®] ER (oxymorphone ER) may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Avoid the use of this agent in patients with impaired consciousness or coma.</p> <p>Difficulty swallowing and risk for obstruction in patients at risk for a small gastrointestinal (GI) lumen; There have been post-marketing reports of difficulty in swallowing Opana[®] ER (oxymorphone ER) tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.</p> <p>There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small GI lumen are at greater risk of developing these complications. Alternative analgesics should be considered in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small GI lumen.</p> <p>Gastrointestinal conditions; Avoid the use of Opana[®] ER (oxymorphone ER) in patients with other GI obstruction. This agent is contraindicated in the presence of paralytic ileus. Oxymorphone may cause spasm of the sphincter of Oddi. Monitor</p>
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	patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. Opioids may also cause increases in the serum amylase.
	Convulsive or seizure disorders; Oxymorphone may exacerbate seizures in patients with seizure disorders, and may induce or aggravate seizures. Monitor patients with a history of seizure disorders for worsened seizure control during treatment with this agent.
	Avoidance of withdrawal; Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic such as Opana® ER (oxymorphone ER) as these agents can reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing therapy, gradually taper the dose. Do not abruptly discontinue medication.
	Driving and operating machinery; Opioids may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Counsel patients not to drive or operate dangerous machinery unless they are tolerant to the effects and know how they will react to the medication.

Due to the potential for addiction, abuse, and misuse, the potential for life-threatening respiratory depression, the possibility of accidental ingestion, the risks of neonatal opioid withdrawal syndrome, and the significant interaction with alcohol consumption, this product also has a Black Box Warning.

Black Box Warning¹

WARNING	
<u>Addiction, Abuse, and Misuse</u>	Opana ER® (oxymorphone ER) exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Opana ER (oxymorphone ER), and monitor all patients regularly for the development of these behaviors or conditions.
<u>Life-threatening Respiratory Depression</u>	Serious, life-threatening, or fatal respiratory depression may occur with use of Opana ER (oxymorphone ER). Monitor for respiratory depression, especially during initiation of Opana ER (oxymorphone ER) or following a dose increase. Instruct patients to swallow Opana ER (oxymorphone ER) capsules whole; crushing, chewing, or dissolving Opana ER (oxymorphone ER) can cause rapid release and absorption of a potentially fatal dose of oxymorphone.
<u>Accidental Ingestion</u>	Accidental ingestion of even one dose of Opana ER (oxymorphone ER), especially by children, can result in a fatal overdose of oxymorphone.
<u>Neonatal Opioid Withdrawal Syndrome</u>	Prolonged use of Opana ER (oxymorphone ER) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
<u>Interaction with Alcohol</u>	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Opana ER (oxymorphone ER). The co-ingestion of alcohol with Opana ER (oxymorphone ER) may result in increased plasma levels and a potentially fatal overdose of

WARNING

oxymorphone.

Contraindications

Opana® ER (oxymorphone ER) is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma or hypercarbia, known or suspected paralytic ileus and gastrointestinal obstruction, moderate and severe hepatic impairment, or a known hypersensitivity (e.g., anaphylaxis) to oxymorphone, any other ingredients in Opana® ER (oxymorphone ER), or to morphine analogues such as codeine.¹

Adverse Drug Events

The safety of Opana® ER (oxymorphone ER) was evaluated in 2,011 patients with moderate to severe chronic non-malignant pain, cancer pain and post-surgical pain from open-label and controlled clinical trials. The most common serious adverse events reported with Opana® ER (oxymorphone ER) included chest pain, pneumonia and vomiting.¹

Table 7. Treatment-Emergent Adverse Reactions Reported by ≥ 5% of Subjects During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term- 12-Week Study in Opioid-Naïve Subjects with Low Back Pain¹

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone ER Tablets	Oxymorphone ER Tablets	Placebo
Preferred Term	(N=325); n (%)	(N=105); n (%)	(N=100); n (%)
Constipation	26	7	1
Dizziness	11	5	3
Headache	11	4	2
Nausea	18	11	9
Pruritus	7	3	1
Somnolence	19	2	0

Table 8. Treatment-Emergent Adverse Reactions Reported by ≥ 5% of Subjects During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term- 12-Week Study in Opioid-Experienced Subjects with Low Back Pain¹

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone ER Tablets	Oxymorphone ER Tablets	Placebo
Preferred Term	(N=250); n (%)	(N=70); n (%)	(N=72); n (%)
Constipation	12	6	1
Dizziness	6	0	0
Headache	12	3	0
Nausea	20	3	1
Pruritus	8	0	0
Somnolence	11	3	0

The most common adverse drug reactions with Opana® ER (oxymorphone ER) in the clinical trials organized by Medical Dictionary for Regulatory Activities (MedDRA's) System Organ Class include: blurred vision, diarrhea, abdominal pain, dyspepsia, dry mouth, decreased appetite, fatigue, lethargy, dehydration, decreased weight, edema, insomnia, anxiety, confusion, restlessness, depression, dyspnea, flushing and hypertension.¹

Postmarketing experience:

The following adverse reactions have been identified during post approval use of Opana® ER (oxymorphone ER): amnesia, convulsion and memory impairment.¹

Drug Interactions**Table 9. Drug and Food Interactions^{1,2}**

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
Naltrexone	Contraindicated	Concurrent use of naltrexone with opioids may result in precipitation of opioid withdrawal symptoms due to decreased opioid effectiveness.
Alcohol (ethanol)	Major	Concomitant use of alcohol may result in increased oxymorphone plasma levels and potentially fatal overdose of oxymorphone. Counsel patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol.
Central nervous system (CNS) Depressants (e.g., sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, alcohol, etc.)	Major	Caution should be used in patients concurrently taking other CNS depressants as they can increase the risk of respiratory depression, profound sedation, coma, and death. When used together, the dose of one or both agents should be reduced. Assess the duration of use of the CNS depressant and individual response, including the degree of tolerance that has developed to CNS depression. Start with Opana® ER (oxymorphone ER) 5 mg every 12 hours, monitor closely, and consider using a lower dose of the concomitant CNS depressant.
Mixed Agonist/Antagonist (pentazocine, nalbuphine, & butorphanol) and Partial Agonist (e.g., buprenorphine) Opioid Analgesics	Major	Concomitant use of mixed agonist/antagonist with opioids or partial agonists may reduce the analgesic effect and/or may precipitate withdrawal symptoms. Avoid concomitant administration.
Muscle Relaxants	Major	Oxymorphone may result in enhanced neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Cimetidine	Major	Cimetidine may potentiate opioid-induced respiratory depression.
Anticholinergics	Major	An increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus, may result from concurrent use with anticholinergics or other medications with anticholinergic activity.
Carbinoxamine	Major	Concurrent use may result in increased risk of paralytic ileus, increased risk of respiratory depression as well as CNS depression.
Meclizine	Major	Concurrent use may result in increased risk of paralytic ileus and increased risk of respiratory and CNS depression.
Loxapine	Major	Concurrent use may result in increased risk of paralytic ileus, increased risk of respiratory depression as well as CNS

		depression.
Ginseng	Moderate	Concurrent use may result in reduced opioid analgesic effectiveness.
Kava	Moderate	Concurrent use may result in increased central nervous system depression.
Valerian	Moderate	Concurrent use may result in additive central nervous system depression.
Food	Moderate	Concurrent use may result in increased oxymorphone exposure and plasma concentrations.

*Severity rating per Micromedex

Patient Monitoring Guidelines^{1,2}

Assess each patient's risk for opioid addiction, abuse, or misuse prior to initiating therapy and monitor all patients for the development of these behaviors or conditions. "Drug seeking" behaviors should also be monitored to help identify these potential concerns.

Continually re-evaluate patients to assess the maintenance of pain control and the development of adverse reactions. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

Continuously monitor patients for new or worsening adverse events or changes in medication efficacy, particularly with changes in drug doses and/or frequency. Closely monitor patients when there is the addition or elimination of other agents that may alter the efficacy or adverse event profile of the interacting agent(s). Individuals with renal and/or hepatic impairment as well as the elderly should have initial doses adjusted to account for impaired ability to metabolize and eliminate oxymorphone and its metabolites. These individuals should be closely monitored as there is the increased risk of adverse events, particularly with changes in the underlying disease impairment and/or dose adjustments.

The following signs and symptoms should be monitored during therapy with opioids:

- respiratory depression and sedation; following treatment initiation and after dose increases; and particularly in high risk patient (elderly, cachectic, and debilitated patients and those with preexisting respiratory depression or otherwise significantly reduced respiratory reserve)
- exacerbation of biliary tract disease, including acute pancreatitis, in patients with a medical history of these disorders
- hypotension; in ambulatory patients; on initiation and with dose titration; especially when ability to maintain blood pressure is compromised
- worsened seizure control; in patients with a history of seizure disorders
- CNS depression

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