***Drug Monograph***

**Generic Name**: oxycodone extended-release

**Trade Name:** OxyContin®

**Dosage Form**:10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg Tablets

**National Drug Codes (NDC#)** 10 mg: (59011-410-10, 59011-410-20), 15 mg: (59011-415-10, 59011-415-20), 20 mg: (59011-420-10, 59011-420-20), 30 mg: (59011-430-10, 59011-430-20), 40 mg: (59011-440-10, 59011-440-20), 60 mg: (59011-460-10, 59011-460-20), 80 mg: (59011-480-10, 59011-480-20)

**Manufacturer**: Purdue Pharma LP

**ADF Product Classification:** Physical/ Chemical barrier

**Executive Summary**

OxyContin® (oxycodone 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, secondary to its relatively new abuse-deterrent formulation (ADF) labeling.

This agent is an extended-release (ER) formulation of oxycodone that is approved by the Food and Drug Administration (FDA) to treat pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It is approved for use in both adults and opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.1-3

OxyContin® (oxycodone ER) is a full opioid agonist that is relatively selective for the µ receptors, which are found in large numbers within the central nervous system. The binding of OxyContin® (oxycodone ER) to µ receptors produces a variety of other potential unwanted side effects including bradycardia, sedation, euphoria, physical dependence, and potentially respiratory depression. 1-3 The efficacy of OxyContin® (oxycodone ER) has been demonstrated in multiple studies for cancer-related pain, osteoarthritis-related pain, low back pain, pain associated with diabetic neuropathy, pain associated with post-herpetic neuralgia as well as post-operative pain.4-41 Of note, all of these safety and efficacy studies in adult patients utilized the original OxyContin® (oxycodone ER) tablet formulation.

This product was first approved for marketing in December 1995. Post-marketing information with the original OxyContin® (oxycodone ER) tablet revealed that it was readily crushable and that there was an increasing prevalence of non-oral abuse (snorting, intravenous, smoking, etc.) following manipulation intended to defeat the extended-release properties of the product.42-44 Such manipulation caused the drug to be released more rapidly, which increased the risk of serious adverse events, including overdose and death.45 Purdue Pharma LP elected to reformulate this product in an effort to make the tablet more difficult to manipulate for the purpose of intentional abuse by various routes of administration (e.g., snorting and intravenous injection) or misuse by inadvertent medication error (e.g., crushing or cutting a tablet). This reformulation was approved by the FDA on April 5, 2010 with new abuse deterrent labeling claims, indicating that the product is formulated with physicochemical barriers to abuse and is expected to result in a meaningful reduction in abuse.45,46 As of August 2010, Purdue stopped shipping the original OxyContin® (oxycodone ER) formulation and began exclusively shipping reformulated OxyContin® (oxycodone ER).2

The reformulated OxyContin® (oxycodone ER) is designed to be bioequivalent to the original formulation.2 It utilizes the RESISTEC® technology that employs a combination of polymer and processing that gives tablet hardness, imparts viscosity when dissolved in aqueous solutions and resists increased drug release rate when mixed with alcoholic beverages.2

As stated in the OxyContin® (oxycodone ER) full prescribing information, there were several abuse deterrence studies that were performed in order to test the effectiveness of this newly formulated product. 47-49 Results support that, relative to original OxyContin® (OC) there is an increase in the ability of the reformulated product (ORF) to resist crushing, breaking, extraction and dissolution in small volumes using a variety of tools and solvents. When subjected to small volumes of an aqueous environment, ORF gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.47 In addition, a crushed formulation of ORF was rated lower than the crushed formulation of OC and oxycodone powder (Oxy API) when administered intranasally on various Overall Drug Liking and Take Drug Again scores. There were also more reports of intranasal irritation with the ORF formulations.48,49

Based on the results from these trials, the FDA determined that the physical and chemical properties of the reformulated OxyContin® (oxycodone ER) product are expected to make the product difficult to inject and to reduce abuse via snorting. However, it also acknowledges that abuse of OxyContin® (oxycodone ER) by these routes, as well as the oral route, is still possible.45

A trial was recently published comparing the effect of tampering on the oral PK profiles of the reformulated OxyContin® (oxycodone ER) as well as another abuse-deterrent ER oxycodone product, Oxycodone DETERx®, now referred to as Xtampza ER® which was recently granted a tentative approval by the FDA in November 2015.50 Approval of this agent is tentative at this time pending patent infringement litigation with Purdue Pharma LP.51 This trial revealed some conflicting data regarding the PK profile of crushed reformulated OxyContin® (oxycodone ER) compared to the two previously mentioned studies. It was observed that both crushed and intact Oxycodone DETERx® resulted in lower Cmax when compared to immediate-release (IR) oxycodone and that the median Tmax for Oxycodone DETERx® appeared unchanged by the act of crushing. This was in contrast to the crushed reformulated OxyContin® (oxycodone ER) which was shown to lose some of its controlled-release properties after manipulation and to be more bioequivalent to IR oxycodone than to the original intact formulation. 50

Although there have been a number of systematic studies that have shown that the reformulation of OxyContin® (oxycodone ER) has been highly effective in reducing the abuse of this product initially, there has also been some documentation that this has not deterred all abuse of OxyContin® (oxycodone ER).52-56 One study, in particular, looked at data from the ongoing Survey of Key Informants’ Patients program, part of the Researched Abuse, Diversion and Addiction-Related Surveillance system that collects and analyzes postmarketing data on misuse and diversion of prescription opioid analgesics and heroin. This study showed that there was a significant initial reduction in past-month abuse after the introduction of the reformulated OxyContin® (oxycodone ER) but that this leveled off with time. In addition, survey data from participants who indicated experience using pre-ADF and ADF OxyContin® (oxycodone ER), reflected three phenomena: (1) a transition from nonoral routes of administration to oral use of ADF OxyContin® (38 participants [43%]); (2) successful efforts to defeat the ADF mechanism leading to a continuation of inhaled or injected use (30 participants [34%]); and (3) exclusive use of the oral route independent of formulation type (20 participants [23%]).57

**Reference Data**

Oxycodone hydrochloride is a full opioid agonist that is relatively selective for the µ receptor. It can, however, bind to other opioid receptors at higher doses. Oxycodone is an analgesic with several actions qualitatively similar to those of morphine. Although the precise mechanism of action is unknown, specific central nervous system (CNS) opioid receptors for endogenous compounds with opioid-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.1-3

The new reformulated OxyContin® (oxycodone ER) has two FDA-approved abuse-deterrent labeling claims indicating that the product is formulated with physicochemical barriers to abuse and is expected to result in a meaningful reduction in abuse.58 However, it is acknowledged that the abuse of this agent by the intravenous, intranasal, and oral routes is still possible. This agent utilizes a matrix drug delivery system so that the active pharmaceutical ingredient and ingredient(s) that control the rate of release of the active ingredient are uniformly distributed throughout the dosage form. Each tablet is controlled by the polyethylene oxide excipient (in this case, a retardant). When subjected to an aqueous environment, polyethylene oxide gradually swells and forms a viscous hydrogel. This hydrogel controls the rate of drug release from the dosage form. The release of active medication, oxycodone, is independent of surrounding pH. These tablets are designed to provide oxycodone delivery over a 12-hour period of time, allowing for every-12-hour dosing. This agent is also formulated with RESISTEC® technology. RESISTEC® uses a unique combination of polymer and processing that (1) confers tablet hardness (2) imparts viscosity when dissolved in aqueous solutions and (3) resists increased drug release rate when mixed with alcoholic beverages, in vitro. These physicochemical attributes are intended to make the tablets more difficult to manipulate for the purpose of misuse and abuse by various routes of administration and to reduce the likelihood of certain inadvertent medication errors.2

In addition to OxyContin® (oxycodone ER), there are multiple other long-acting opioids available on the market. Some of these products are also listed as having abuse-deterrent properties.3 A list of these medications is shown below in Table1.

**Table 1. Long-Acting Opioid Availability59**

| **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**

OxyContin® (oxycodone 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. On August 13, 2015, the Food and Drug Administration (FDA) approved a supplemental NDA (sNDA) for the Full Prescribing Information to include labeling for a pediatric indication in opioid-tolerant pediatric patients 11 years of age and older. Thus, OxyContin® (oxycodone ER) is now also 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 opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.1-3

More than 2,000 adult patients have been enrolled in OxyContin® (oxycodone ER) clinical studies, some in more than one study. These studies consisted of double-blind, randomized studies and open-label trials including patients with cancer- and noncancer-related pain syndromes. All of the OxyContin® (oxycodone ER) clinical studies for adult patients utilized the original OxyContin® tablet formulation and many were placebo-controlled trials for which OxyContin® (oxycodone ER) demonstrated superior efficacy over placebo for management of pain.4-41 For the purposes of this report, the two clinical trials that are reported in the package insert will be described in further detail.

The first trial was a double-blind, placebo-controlled, fixed-dose, parallel group, two-week study that was conducted in 133 adult patients with persistent, moderate to severe osteoarthritis pain, who were judged as having inadequate pain control with their current therapy. Individuals were randomized to double-blind treatment with placebo (N=45), 10 mg OxyContin® (oxycodone ER) (N=44) or 20 mg OxyContin® (oxycodone ER) (N=44) every 12 hours for 14 days. The use of the OxyContin® 20 mg tablet was found to be superior (P<0.05) to placebo in reducing pain intensity and the interference of pain with mood, sleep and enjoyment of life. However, the OxyContin® (oxycodone ER) 10 mg dose was not found to be statistically significant in pain reduction compared with placebo. 60

The second trial was an open-label clinical trial of 155 opioid-tolerant pediatric patients aged 6 to 16 years old with moderate to severe malignant and/or nonmalignant chronic pain requiring opioid analgesics. The starting total daily doses of OxyContin® (oxycodone ER) ranged from 20 to 100 mg based on the patient’s prior opioid dose. The mean daily dose was 33.30 mg (range 20 to 140 mg/day). The mean duration of therapy was 20.7 days (range 1 to 43 days). The results from the trial demonstrated that OxyContin®(oxycodone ER), alone or in combination with supplemental analgesics, reduced or maintained pain right now scores from baseline to week four. Too few patients less than 11 years of age were enrolled in the clinical trial to provide meaningful safety data in this age group. The most frequent adverse events observed in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation. The full results of this phase III clinical trial are currently unpublished.61

The newly formulated OxyContin® (oxycodone ER) product (referred in this trial as OP) has also been evaluated in several abuse deterrence studies. The first was an in vitro physical and chemical manipulation study that evaluated the success of different extraction methods for beating the extended-release formulation. Laboratory experiments were targeted toward outcomes that could produce tampered product suitable for administration by alternate routes. Initial experiments were conducted to determine how tablets could be reduced to particles potentially suitable for non-oral administration. Common household devices were tested including pill crushers, mortars and pestles, grinders, and graters. The intact reformulated OP tablet and crushed original oxycodone controlled-release (OC) were included as controls. Studies included, but were not limited to, determining the rate of extraction of oxycodone from physically manipulated OP, determining the feasibility of preparation for injection, and determining the feasibility of abuse viasmoking. Additional experiments explored manipulations such as oven-heating and microwaving. Interpretative criteria for success were generally based on whether a sufficient amount of drug was successfully released that might produce a desired effect.47

Study endpoints were set to help define decision points (>90% release in a controlled standardized testing environment). In the case of oxycodone, in which a known easily abused formulation was being replaced with a formulation designed to be tamper resistant, deterrence was considered achieved if the amount of drug released was considerably less than the original OC product and the manipulation was so difficult and complex that it appeared reasonable to assume that it would not be widely practiced. For this determination, a “deterrent” property was ascribed as the required amounts of experience, time, work, and resources increased substantially over that necessary for manipulation of conventional formulations that were not designed to be tamper-deterrent. Additionally, if a minimum amount of drug considered likely to produce a psychoactive response in a non-tolerant individual (e.g*.*, 5 to 20 mg of oxycodone by the intravenous route) was not released then a second iteration of the study would be considered. If the initial manipulation produced near failure of the formulation (i.e.*,* >90% of oxycodone was released), no further iterations were considered necessary. If OP exhibited deterrence when subjected to an initial manipulation, a variety of changes in experimental design were considered that might enhance drug release (e.g.*,* different pre-treatments, new solvents, pH adjustments, changes in isolation procedures).47

The results of the trial showed that physical manipulations of OP that involved cutting or grinding tablets were considerably more difficult and required more time, effort, and specialized equipment than with OC. Extractions with aqueous based solvents were complicated by the hydro-gelling properties of the OP formulation, particularly when smaller volumes, such as those used in preparation for injection, were employed. The high viscosity of the resulting solutions impaired syringe ability and injectability. More complex extraction schemes occasionally produced greater release of drug, but resulted in preparations that were unsuitable for immediate use. Laboratory experiments designed to simulate smoking conditions produced low recoveries of volatized drug indicating that the OP formulation would be inefficient for abuse via smoking. Dissolution experiments indicated that co-administration of alcoholic beverages with intact or physically manipulated OP formulation would not likely result in dose dumping due to the presence of alcohol.47

Further abuse deterrence trials have also been performed looking at human pharmacokinetic (PK) and clinical abuse potential studies. The first, by Harris et al., was a randomized, double‐blind, positive‐ and placebo‐controlled crossover study that enrolled healthy, adult, nonphysically dependent recreational opioid users with recent history of intranasal drug abuse (N=30). This five‐treatment crossover study evaluated the abuse potential, pharmacodynamics (PD), PKs, and safety profile of finely and coarsely crushed reformulated OxyContin® (ORF) versus original OxyContin® (OC) and oxycodone powder (Oxy API). The study consisted of a screening phase, a qualification phase, a treatment phase, and a follow‐up visit (two to four days following the last treatment visit or after early withdrawal). The screening phase included a naloxone challenge to determine physical dependence. In the qualification phase, subjects self‐administered intranasal doses of 30 mg Oxy API and volume‐matched lactose powder placebo in a randomized crossover fashion, with approximately 24 hours between administrations. Subjects were eligible to enter the double‐blind treatment phase if they tolerated 30 mg Oxy API. In the double‐blind treatment phase, subjects self‐ administered intranasal doses of the five study treatments in a randomized crossover fashion, with a washout period of at least 48 hours between treatments. The five treatments were lactose powder OC placebo, 30 mg finely crushed ORF, 30 mg coarsely crushed ORF, 30 mg finely crushed OC, and 30 mg Oxy API powder. Results from the study revealed that crushed ORF administration yielded reduced oxycodone Cmax and increased Tmax versus crushed OC and Oxy API. Peak effects for pharmacodynamic measures were delayed with ORF (one to two hours) versus OC and Oxy API (0.5 to 1 hour). Overall Drug Liking (ODL), Take Drug Again (TDA), High Visual Analog (VAS), and Subjective Drug Value (SDV) Emax values were significantly lower (P≤0.05) and some intranasal irritation ratings were greater for ORF versus OC and Oxy API. No significant or unexpected safety findings were observed. Compared with OC and Oxy API, intranasally administered ORF was associated with lower and delayed peak plasma concentrations, decreased drug‐liking, and decreased intranasal tolerability.48

The second human abuse-deterrence trial, by Perrino et al., was a randomized, single-blind, single-dose, single-center, six-sequence, triple-treatment, triple-period crossover study that enrolled eligible healthy adults (aged 18 to 55 years) with no clinically significant medical history. Special preference for study enrollment was given to recreational drug users who had experience with opioid use on at least five occasions, and to subjects who reported at least three occasions of intranasal opioid use for the purpose of abuse or misuse within the past year. The study was designed to evaluate the PKs, tolerability, and safety of intranasally administered ORF, both finely crushed (10 mg) and coarsely crushed (10 mg), as well as finely crushed OC (10 mg). Of 83 subjects screened and enrolled, 30 were randomized. The study duration was up to 42 days; a 28-day screening phase was followed by a 7-day treatment phase, with follow-up three to seven days after the last dose of study drug. Subjects were randomized to a treatment sequence on the morning of day one and received treatments on days one, three and five of the treatment phase, with a minimum washout period of 48 hours between dose administrations. For each treatment period, subjects completed a 10-hour overnight fast before sitting in an upright position and intranasally insufflating a dose of finely crushed ORF (10 mg), coarsely crushed ORF (10 mg), or finely crushed OC (10 mg) through a short thin straw. Subjects continued fasting for four hours subsequent to dosing and were to remain upright, unless a procedure required that they be in the supine position. They remained confined to the study site throughout all three treatment periods. Treatment procedures were identical for all three treatment periods, with subjects receiving single intranasal doses of study drug in alternating nares (e.g., left-right-left). Telephone follow-ups were conducted three to seven days after the last dose or following early discontinuation. Results observed during the study included a mean Cmax that was lower for finely crushed ORF and coarsely crushed ORF than that for finely crushed OC values, median Tmax values that were higher for finely crushed ORF and coarsely crushed ORF compared to finely crushed OC and mean AQ scores for finely crushed ORF and coarsely crushed ARF that were approximately 66 to 80% lower than finely crushed OC. In addition there was an increased nasal intolerability with the ORF product than with the OC. The safety profile of ORF was similar to that of OC. Most adverse events (AEs) for all treatments were classified as mild or moderate and were those commonly associated with opioid use (e.g., nausea, vomiting, and headache).49

The final trial was a randomized, open-label, single-dose, five-treatment, active-controlled, naltrexone-blocked, crossover comparison study. This cross-over study included a 21-day Screening Phase, followed by a five-period treatment phase in which subjects received single oral doses of intact Oxycodone DETERx® 40 mg (expressed as HCl equivalents), crushed Oxycodone DETERx® 40 mg, intact OxyContin® (oxycodone ER) 40 mg, crushed OxyContin® (oxycodone ER) 40 mg, and crushed IR oxycodone 40 mg in a randomized order. At each of the five treatment periods, subjects were admitted to the research unit the day before dosing at which time they received an oral dose of 50 mg naltrexone (approximately 13 hours prior to dosing) to ensure that they were able to tolerate the naltrexone dose. If subjects were able to tolerate the naltrexone, they were given a second 50 mg dose of naltrexone one hour prior to study drug dosing as a safety precaution. There was a minimum five-day washout period between each dose of study drug. Primary endpoints that were evaluated during this study included PK parameters such as plasma oxycodone concentrations prior to dosing and postdose Cmax, Tmax, AUCinf, AQ) and safety monitoring. Results showed that manipulation of Oxycodone DETERx® did not significantly change the oxycodone PK profile when compared with intact Oxycodone DETERx®; the crushed and intact products were bioequivalent with no significant difference in Tmax. Consistent with these findings, AQ values were comparable for crushed and intact Oxycodone DETERx® treatments, and were much lower compared with crushed IR oxycodone. In contrast, crushing reformulated OxyContin® (oxycodone ER) resulted in a significantly higher Cmax and shorter median Tmax compared with intact OxyContin® (oxycodone ER). Moreover, the early plasma exposure profile, as measured by cumulative PAUC up to 1.75 hours, was markedly different for crushed and intact OxyContin® (oxycodone ER); therefore, crushed reformulated OxyContin® (oxycodone ER) was bioequivalent to crushed IR oxycodone, but not to intact OxyContin® (oxycodone ER).50

**Table 2. Clinical Trials**

| **Study and Drug Regimen** | **Study Design and**  **Demographics** | **Sample Size**  **and Study Duration** | **End Points** | **Results** |
| --- | --- | --- | --- | --- |
| Roth et al60  OxyContin® (oxycodone ER) 10 mg Q12H  vs  OxyContin® (oxycodone ER) 20 mg Q12H  vs  placebo | DB, PG, RCT  Patients ≥18 years of age with a confirmed diagnosis of OA, experiencing frequent or persistent pain for at least one month, current daily pain intensity moderate or greater | N=133  14 days | Primary:  Pain intensity  Secondary:  Interference of pain on daily activities BPI, quality of sleep, Activities and Lifestyles Questionnaire, safety (AEs), number of night awakenings due to pain | Primary:  Compared to placebo, the use of OxyContin® (oxycodone ER) 20 mg significantly reduced pain intensity (P<0.05) as well as interference of pain with mood, sleep and enjoyment of life (P<0.05).  Secondary:  The 20 mg OxyContin® (oxycodone ER) group showed significant mean improvements from baseline in mitigating the interference of pain on mood, sleep and enjoyment of life (P<0.05).  Interference of pain on walking ability, general activity, normal work and relations with others showed some improvement from baseline but did not reach statistical significance. The 10 mg OxyContin® (oxycodone ER) group showed larger improvement than did the placebo group for pain and function, but differences were not statistically significant.  Eighty-seven (65.4%) of patients reported at least one treatment-related AE during the study however, none were deemed life-threatening.  Treatment-related AEs occurring in ≥10% of patients receiving OxyContin® (oxycodone ER) included nausea, constipation, somnolence, vomiting, pruritus and headache. |
| NCT0119229561\*  OxyContin® (oxycodone ER) Q12H, variable (maximum of 140 mg/day) | OL, MC  Opioid-tolerant (defined as having received treatment with opioids for at least five consecutive days prior to dosing and with at least 20 mg daily of oxycodone or the equivalent during at least the last 48 hours prior to start of OxyContin® [oxycodone ER]) pediatric patients 6 to 16 years of age with moderate to severe malignant and/or nonmalignant chronic pain requiring opioid therapy | N=155  5 Weeks | Primary:  Safety assessments- AEs, physical examinations, clinical laboratory evaluations, vital signs, pulse oximetry and somnolence using the UMSS  Secondary:  Efficacy assessments- pain right now assessed by patients at time of dosing using the FPS-R, for patients aged 6 to < 12 years, or the 100 mm VAS for patients aged 12 to 16 years, use of supplemental pain medication, parent/caregiver-assessed FDI at baseline, week two and week four, early discontinuation and PGIC at the final visit | Primary:  The mean daily dose of OxyContin® (oxycodone ER) was 33.3 mg/day. For all age groups, OxyContin® (oxycodone ER) dose from week one to week four was relatively stable, with downward titration of dose (32.3%) being more common than upward titration (16.1%).  The mean number of days on OxyContin® (oxycodone ER) was 20.7 (range: 1 to 43 days) and was similar for both age groups. In an extension study, 23 of the 155 patients who completed four weeks of treatment in the core study and were deemed appropriate for continued treatment with OxyContin® (oxycodone ER) in the opinion of the study physician were treated beyond four weeks, including 13 who were treated for 28 weeks.  TEAEs were reported for 108 patients (69.7%), with similar rates in both age groups. There were four (2.6%) deaths, all in patients who had malignant neoplasm. Their deaths were not considered to be related to OxyContin® (oxycodone ER). A total of 24 (15.5%) patients experienced SAEs. No more than six patients experienced any individual SAE.  Two older patients had a UMSS score of 3 after the first dose of OxyContin® (oxycodone ER). A UMSS score of 3 indicates a patient who is in deep sleep that arouses to deeper physical stimulus (range 0 to 4, 0 = awake and alert, 4 = unarousable). There were no other UMSS scores ≥ 3 reported during the trial.  The majority of patients stayed within the normal range for hematologic and blood chemistry parameter values during the study.  There were no clinically significant changes in blood pressure or pulse rate from baseline to the end of the study. Two patients (one from each age group) had a clinically significant pulse oximetry finding. Neither event resulted in dose reduction or discontinuation.  Secondary:  Scoring for the FPS-R used for the younger age group ranged from 0 to 10, where 0 represents “no pain/ hurt” and 10 represents “very much pain/ hurts worst.” Scoring for the VAS ranged from 0 to 100, where 0 represents “no pain” and 100 represents “pain as bad as it could be.” The baseline pain right now scores indicated that patients had acceptable pain control at study entry.  In the younger age group, the mean (SD) weekly average pain right now scores (based on the FPS-R) at week 4 improved from 4.44 (3.25) at baseline to 3.13 (2.57) in the morning and to 3.42 (2.97) in the evening. In the older age group, the mean (SD) weekly average pain right now scores (based on the VAS) at week 4 improved from 44.58 (28.29) at baseline to 35.58 (27.18) in the morning and to 35.30 (26.71) in the evening. Overall, OxyContin® (oxycodone ER), alone or in combination with supplemental analgesics, reduced or maintained pain right now scores from baseline to week four.  The majority of all patients took supplemental pain medication sometime during the study (136 patients, 87.7%). The most frequently used supplemental opioid medications were hydrocodone and oxycodone. The most frequently used nonopioid supplemental medications were ibuprofen and gabapentin.  For the overall population and both age groups, the mean total FDI scores at week 4 or study discontinuation decreased from those at baseline, indicating less functional disability. In the overall population, 71.6% had PGIC scores of 1 or 2 indicating very much improved or much improved; similar results were seen in each age group. |
| Harris et al48  Finely-crushed reformulated OxyContin (ORF) 30 mg tablets  vs  coarsely-crushed ORF 30 mg  finely-crushed original OxyContin (OC) 30 mg  vs  oxycodone powder 30 mg (Oxy API)  vs  lactose powder OC placebo | DB, positive and PCT, RCT, XO  Adult, nonphysically dependent, healthy, recreational opioid users aged 18 to 55 years who reported a history of nonmedical use of opioids via the intranasal route | N=30  Approx-imately 2 weeks | Primary:  PK, PD,ODL, TDA and High VAS; SDV, pupillometry, intranasal irritation and safety assessed to 24 hours postdose  Secondary:  Not reported | Primary:  For the pharmacokinetic parameters, there was found to be incomplete dosing in nine of the 28 receiving ORF-C (32%), 10/29 subjects receiving ORF‐F (34%), 2/28 subjects receiving OC (7%), 0/29 subjects receiving Oxy API, and 3/29 subjects receiving OC placebo (10%). Cmax values were lower for finely and coarsely crushed ORF than for OC and Oxy API. Median Tmax values for finely and coarsely crushed ORF were approximately twice as long as those observed for OC and Oxy API. Mean AUCinf values were comparable across all active treatments. Median t1/2 values were somewhat higher and more variable for finely and coarsely crushed ORF compared with that of OC and Oxy API. Abuse quotients were fivefold higher for Oxy API and OC (102.15 and 94.75 ng/mL/h, respectively) compared with finely and coarsely crushed ORF (17.57 and 16.96 ng/mL/h, respectively). P values not reported for above.  AQ for finely and coarsely crushed ORF were significantly lower (P< 0.0001) than crushed Oxy API and OC.  In regards to the PD parameters, responses were largest for the positive controls, smallest for OC placebo, and intermediate for finely and coarsely crushed ORF, with finely crushed ORF generally showing larger responses than coarsely crushed ORF.  In regards to pupillometry, intranasal administration of Oxy API and OC resulted in oxycodone‐induced miosis (i.e., reduced pupil size) that peaked at 0.5 to 1 hour postdose versus OC placebo. Mean pupil size then increased slightly beginning at 3 hours postdose. No notable differences were observed in pupil‐size scores across time with OC placebo treatment.  During the qualification phase, subjects demonstrated the ability to distinguish between Oxy API and OC placebo treatments. During the treatment phase, both Drug Liking and High VAS, Emax responses were highest for the positive controls, and these occurred within one hour postdose. The positive controls showed comparable peak scores and time courses. Lower peak responses were seen with both finely and coarsely crushed ORF, and these occurred later than for the positive controls. Responses for the positive controls and for ORF were all higher than for OC placebo. The peak response and time course of coarsely crushed ORF were lower than for finely crushed ORF.  For ODL VAS, TDA VAS, and SDV, responses remained relatively consistent at eight and 24 hours postdose. All active treatments had Emax values that were significantly greater versus OC placebo (P= 0.003) except coarsely crushed ORF, which did not differ from OC placebo on ODL (P= 0.07). Finely and coarsely crushed ORF had significantly lower Emax values versus positive controls for all three global measures of drug effect (P=0.002). Emax values for finely and coarsely crushed ORF did not differ significantly from each other on TDA VAS and SDV. The Emax value for ODL VAS was significantly lower for coarsely crushed versus finely crushed ORF (P=0.043).  The pattern of responses for High VAS and Good Effects VAS proved similar for both positive controls; both treatments demonstrated prominent, statistically significant responses versus OC placebo (P< 0.001 for all). ORF scores were intermediate, and OC placebo scores were the lowest.  For intranasal tolerability, greater nasal irritation was seen with coarsely and finely crushed ORF. Compared to OC placebo, finely crushed ORF had significantly higher Emax on measures of Need to Blow Nose (P=0.017) and Nasal Congestion (P=0.014), whereas Oxy API, OC, and coarsely crushed ORF did not. Compared to Oxy API, both finely and coarsely crushed ORF had significantly higher Emax on both of these measures (P< 0.01 for all comparisons). Compared to OC, finely crushed ORF had significantly higher Emax on both measures, and coarsely crushed ORF had significantly higher Emax for Nasal Congestion only (P=0.001).  For the safety component, no deaths, severe TEAEs, or other serious AEs occurred. The overall incidence of reported TEAEs, from highest to lowest incidence, was 96.4% for finely crushed OC and 89.7% for Oxy API (positive controls), 86.2% for finely crushed ORF, 75.0% for coarsely crushed ORF, and 41.4% for OC placebo. Most TEAEs were of mild intensity. One subject experienced a moderately intense TEAE (respiratory depression following finely crushed OC intranasal administration).  Secondary:  Not reported. |
| Perrino et al49  Finely crushed reformulated OxyContin® (oxycodone ER) (ORF) 10 mg  vs.  coarsely crushed ORF 10 mg  vs.  finely crushed original formulation OxyContin® (oxycodone ER) (OC)  10 mg | RCT, single-blind, single-center, six-sequence, triple-treatment, triple-period XO  Adult, nonphysically dependent, healthy, recreational opioid users aged 18 to 55 years who reported a history of nonmedical use of opioids on at least five occasions or at least three occasions of intranasal opioid use within the past year | N=30  Up to 42 days  (28-day screening phase followed by a seven-day treatment phase, with follow-up three to seven days after last dose of study drug) | Primary:  PK (Cmax, tmax, AUClast, AUCinf, AQ, intranasal tolerability and safety (AEs, vital signs, pulse oximetry [SpO2] and ECG  Secondary:  Not reported | Primary:  Mean Cmax values for finely crushed ORF (17.1 ng/mL) and coarsely crushed ORF (15.5 ng/mL) were lower than that for finely crushed OC (22.2 ng/mL). Median tmax for finely crushed OC (1.0 hour) was shorter than that for either finely crushed ORF (2.0 hour) or coarsely crushed ORF (3.0 hour).  Mean AQ values were approximately 66% and 80% lower, respectively, for finely crushed ORF and coarsely crushed ORF than that for finely crushed OC.  Finely crushed ORF, coarsely crushed ORF, and finely crushed OC demonstrated similar total oxycodone exposures (AUCinf); (124 ng\*h/mL, 134 ng\*h/mL and 128 ng\*h/mL respectively).  In contrast to OC, both finely and coarsely crushed ORF retained some control of oxycodone release.  Insufflation of ORF produced greater nasal discomfort (P=0.0030 for finely crushed ORF, P<0.0001 for coarsely crushed ORF) and stuffiness (P<0.0001 for both) than finely crushed OC. The finely crushed OC produced higher runny nose scores.  The most commonly reported AEs were headache, nausea and vomiting and most AEs were mild to moderate in severity.  Results of laboratory tests, vital signs measurements, SpO2 evaluations, and ECG recordings revealed no clinically significant abnormalities and raised no safety concerns for the study treatments.  Secondary:  Not reported. |
| Gudin et al50  Intact Oxycodone DETERx® 40 mg  vs  intact OxyContin® (oxycodone ER) 40 mg  vs  crushed oxycodone DETERx® 40 mg  vs  crushed IR oxycodone (2 x 20 mg tabs)  vs  crushed OxyContin® (oxycodone ER) 40 mg | AC, OL, RCT, XO  Healthy nonphysically dependent adults aged 18 to 50 years, with no clinically significant abnormalities on medical history,  vital signs, physical examination, 12-lead ECG,  or clinical laboratory tests | N=38  Approx-imately 41 days | Primary:  PK (multiple plasma oxycodone concentrations prior to dosing and  postdose for 24 hours for IR oxycodone and  36 hours postdose for intact and  crushed Oxycodone DETERx® and intact and crushed  OxyContin® [oxycodone ER]), Cmax, Tmax, AUCinf, AQ) and safety monitoring (TEAEs, vital signs, O2, physical exams)  Secondary:  Not reported | Primary:  Following oral administration of crushed IR oxycodone with a HFHC meal, there was a rapid initial increase in mean plasma concentrations. The mean Cmax (SD)79.4 ng/mL (17.1) was reached at approximately 1.75 hours after dosing. Oral administration of crushed OxyContin® (oxycodone ER) resulted in a similar rapid rise in plasma oxycodone concentrations with a similar Cmax 78.4 ng/mL (12.9) and Tmax 1.75 hours as the immediate-release (IR) oxycodone product. This was significantly shorter than intact OxyContin® (oxycodone ER) (median difference 3.25 hours; P<0.0001).  This is in contrast to the oral administration of both intact and crushed Oxycodone DETERx® which resulted in a lower and delayed mean Cmax of 67.5 ng/mL (17.6) for the intact product and 62.9 ng/mL (12.6) for the crushed product. The Tmax was observed to be 3.5 hours and 4.00 hours respectively. This longer Tmax for the Oxycodone DETERx® products compared to IR oxycodone (median difference 2.0 hours, P<0.0001).  The most common TEAEs (>5%) that were reported in this study were fatigue and headache following administration of intact Oxycodone DETERx ® (5.3%) and crushed IR oxycodone (7.5%). There were no TEAEs reported following administration of crushed or intact OxyContin® (oxycodone ER). None of the subjects experienced serious TEAEs and none of the subjects were discontinued from the study due to TEAEs. There were no clinically significant treatment-related changes in clinical laboratory results, vital signs, blood oxygen saturations levels or physical examination findings.  Secondary:  Not reported. |

\*Trial is registered on ClinicalTrials.gov

Drug regimen abbreviations: Q12H=every 12 hours

Study abbreviations: AC*=*active-controlled, AE=adverse event, AQ=abuse quotient, AUC=area under the curve, AUCinf=area under the plasma concentration-time curve extrapolated to infinity, AUClast= area under the plasma concentration-time curve from hour 0 to the last measurable plasma concentration, BPI=Brief Pain Inventory, CI=confidence interval, Cmax=maximum observed plasma concentration, CR=controlled-release, DB*=*double-blind, ECG= electrocardiograms, Emax= maximum effect, ER=extended-release, FDI=Functional Disability Inventory, FPS-R=Faces Pain Scale-Revised, HFHC=high-fat, high-calorie, IR=immediate-release, MC=multicenter, OA=osteoarthritis, ODL=Overall Drug Liking, OL*=*open-label, PAUC=partial area under the plasma concentration-time curve, PC*=*placebo-controlled, PD= pharmacodynamic, PG*=*parallel-group, PGIC=parent/caregiver-assessed global impression of change, PK=pharmacokinetic, RCT*=*randomized controlled trial, SAE=serious adverse event, SD=standard deviation, SDV=Subjective Drug Value, T1/2= terminal elimination half-life, TDA=Take Drug Again, TEAE=treatment-emergent adverse event, Tmax=time to reach maximum plasma concentration, UMSS=University of Michigan Sedation Scale, VAS=visual analog scale, XO*=*crossover

**Pharmacokinetics**

**Table 3. Pharmacokinetics1-3**

| **Generic Name** | **Bioavailability (%)** | **Plasma Protein Binding (%)** | **Volume of Distribution**  **(L/kg)** | **Renal Excretion** | **Active Metabolites** | **Serum Half-Life (hours)** |
| --- | --- | --- | --- | --- | --- | --- |
| Oxycodone ER | 60 to 87 | 45 | 2.6 | oxycodone and its metabolites primarily excreted via the kidneys | Noroxycodone, noroxymorphone and oxymorphone | 4.5 |

*Distribution*

Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk.1-3

*Excretion*

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%.

*Metabolism*

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone. 1-3

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone.1-3

**Pharmacogenomics**

There are no specific pharmacogenomics reported for oxycodone ER. However, there has been some literature to date looking at pharmacogenetics with the opioid class. It has been noted that utilizing pharmacogenetics in clinical practice for the context of pain is challenging, due to the complexity of this multifaceted phenotype and the overall subjective nature of pain perception and response to analgesia. Overall, numerous genes involved with the pharmacokinetics and dynamics of opioids response are candidate genes in the context of opioid analgesia. The clinical relevance of CYP2D6 genotyping to predict analgesic outcomes is still relatively unknown; the two extremes in CYP2D6 genotype (ultrarapid and poor metabolism) seem to predict pain response and/or adverse effects. Overall, the level of evidence linking genetic variability (CYP2D6 and CYP3A4) to oxycodone response and phenotype (altered biotransformation of oxycodone into oxymorphone and overall clearance of oxycodone and oxymorphone) is strong; however, there has been no randomized clinical trial on the benefits of genetic testing prior to oxycodone therapy.62

**Special Populations**

**Table 4. Special Populations** 1-3

| **Population** | **Precaution** |
| --- | --- |
| Elderly | The plasma concentrations of oxycodone are only slightly affected by age, being 15% greater in elderly as compared to young subjects (age 21 to 45).  For geriatric patients who are debilitated and not opioid tolerant, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage cautiously. |
| Renal Dysfunction | In patients with renal impairment (creatinine clearance <60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation. |
| Hepatic Dysfunction | For patients with hepatic impairment, start dosing patients at one-third to one-half the recommended starting dosage followed by careful dosage titration. |
| Pregnancy / Nursing | Pregnancy Category: C\*  There are no adequate and well-controlled studies in pregnant women. Oxycodone should only be used during pregnancy if the potential benefit outweighs the risk to the fetus. Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.  Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving oxycodone due to the possibility of sedation or respiratory depression in the infant. |
| Children | FDA approved for use in children 11 years of age and older.  No evidence of overall differences in systemic exposure of oxycodone was observed between children 11 years of age and older and adult patients. |
| Gender | No special considerations. |
| Race | No special considerations. |

\*No adequate or well-controlled trials.

**Dosage Forms1-3**

**Table 5. Availability, Storage and Handling1**

| **Dosage Form** | **Strength** | **Special Handling or Storage** |
| --- | --- | --- |
| Extended-release tablet | 10 mg  15 mg  20 mg  30 mg  40 mg  60 mg  80 mg | Store at 15 to 30° C (59 to 86° F)  Dispense and store in a tight, light-resistant container. |

**Dosage Range1-3**

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.

***Adults***

Initial dosage in adults who are NOT opioid-tolerant:

OxyContin® (oxycodone ER) 10 mg 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.

Conversion from other oral oxycodone formulations to OxyContin® (oxycodone ER):

If switching from other oral oxycodone formulations to OxyContin® (oxycodone ER), administer one half of the patient's total daily oral oxycodone dose as OxyContin® (oxycodone ER) every 12 hours.

Conversion from other opioids to OxyContin® (oxycodone ER):

There are no established conversion ratios for conversion from other opioids to OxyContin® (oxycodone ER) defined by clinical trials. Discontinue all other around-the-clock opioid drugs when OxyContin® (oxycodone ER) therapy is initiated and initiate dosing using OxyContin® (oxycodone ER) 10 mg orally every 12 hours.

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. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioids.

Conversion from methadone to OxyContin® (oxycodone ER):   
Close monitoring is of particular importance 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.

Conversion from transdermal fentanyl to OxyContin® (oxycodone ER):   
If switching from transdermal fentanyl patch to OxyContin® (oxycodone ER), ensure that the patch has been removed for at least 18 hours prior to starting OxyContin® (oxycodone ER). Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OxyContin® (oxycodone ER) every 12 hours for each 25 µg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OxyContin® (oxycodone ER), as there is limited documented experience with this conversion.

***Elderly***

Dosage modifications in geriatric patients who are debilitated and not opioid-tolerant:

Start dosing patients at 1/3 to 1/2 the recommended starting dosage and titrate the dosage cautiously.

***Pediatrics***

Initial dosage in pediatric patients 11 years and older:

The following dosing information is for use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least five consecutive days. For the two days immediately preceding dosing with OxyContin® (oxycodone ER), patients must be taking a minimum of 20 mg per day of oxycodone or its equivalent. OxyContin® (oxycodone ER) is not appropriate for use in pediatric patients requiring less than a 20 mg total daily dose. Table 5, based on clinical trial experience, displays the conversion factor when switching pediatric patients 11 years and older (under the conditions described above) from opioids to OxyContin® (oxycodone ER).  The conversion factors in this table are only for the conversion from one of the listed oral opioids to OxyContin® (oxycodone ER). The formula for conversion from prior opioids, including oral oxycodone, to the daily dose of OxyContin® (oxycodone ER) is mg per day of prior opioid x factor = mg per day of OxyContin® (oxycodone ER). Divide the calculated total daily dose by 2 to get the every-12-hour OxyContin® (oxycodone ER) dose. If rounding is necessary, always round the dose down to the nearest OxyContin® (oxycodone ER) tablet strength available.

**Table 6. Conversion factors when switching pediatric patients 11 years and older to OxyContin® (oxycodone ER)**

|  |  |  |
| --- | --- | --- |
| **Prior Opioid** | **Conversion Factor** | |
|  | **Oral** | **Parenteral\*** |
| Oxycodone | 1 | - |
| Hydrocodone | 0.9 | - |
| Hydromorphone | 4 | 20 |
| Morphine | 0.5 | 3 |
| Tramadol | 0.17 | 0.2 |

\*For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

Discontinue all other around-the-clock opioid drugs when OxyContin® (oxycodone ER) therapy is initiated.

Step 1: To calculate the estimated total OxyContin® (oxycodone ER) daily dose using Table 4:

* For pediatric patients taking a single opioid, sum the current total daily dosage of the opioid and then multiply the total daily dosage by the approximate conversion factor to calculate the approximate OxyContin® (oxycodone ER) daily dosage.
* For pediatric patients on a regimen of more than one opioid, calculate the approximate oxycodone dose for each opioid and sum the totals to obtain the approximate OxyContin® (oxycodone ER) daily dosage.
* For pediatric patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Step 2: If rounding is necessary, always round the dosage down to the nearest OxyContin® (oxycodone ER) tablet strength available and initiate OxyContin® (oxycodone ER) therapy with that dose. If the calculated OxyContin® (oxycodone ER) total daily dosage is less than 20 mg, there is no safe strength for conversion and do not initiate OxyContin® (oxycodone ER).

Step 3: Close observation and titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to OxyContin® (oxycodone ER).

There is limited experience with conversion from transdermal fentanyl to OxyContin® (oxycodone ER) in pediatric patients 11 years and older. If switching from transdermal fentanyl patch to OxyContin® (oxycodone ER), ensure that the patch has been removed for at least 18 hours prior to starting OxyContin® (oxycodone ER). Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OxyContin® (oxycodone ER) every 12 hours for each 25 µg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OxyContin® (oxycodone ER).

If using asymmetric dosing, instruct patients to take the higher dose in the morning and the lower dose in the evening

Titration and maintenance of therapy in adults and pediatric patients 11 years and older

Individually titrate OxyContin® (oxycodone ER) to a dosage that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OxyContin® (oxycodone ER) to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and 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.

Patients who experience breakthrough pain may require a dosage increase of OxyContin® (oxycodone 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 the OxyContin® (oxycodone ER) dosage. Because steady-state plasma concentrations are approximated in one day, OxyContin® (oxycodone ER) dosage may be adjusted every one to two days. If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline for pediatric patients 11 years and older, the total daily oxycodone dosage usually can be increased by 25% of the current total daily dosage. As a guideline for adults, the total daily oxycodone dosage usually can be increased by 25% to 50% of the current total daily dosage, each time an increase is clinically indicated.

***Hepatic Insufficiency***

For patients with hepatic impairment, start dosing patients at 1/3 to 1/2 the recommended starting dosage followed by careful dosage titration.

***Renal Insufficiency***

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation.

***Special considerations***

Dosage modification in patients with concomitant use of central nervous system (CNS) depressants:

If the patient is currently taking a CNS depressant and the decision is made to begin OxyContin® (oxycodone ER), start with 1/3 to 1/2 the recommended starting dosage of OxyContin® (oxycodone ER) and monitor patients for signs of respiratory depression, sedation, and hypotension.

Administration requirements

OxyContin® (oxycodone ER) tablets must be taken whole, with enough water to ensure complete swallowing immediately after placing in the mouth. If the patient’s dose requires multiple tablets, they should only take one tablet at a time and must not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth.

This medication can be taken without regard to meals as food has no significant effect on the extent of absorption of oxycodone.

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

Discontinuation of OxyContin® (oxycodone ER):

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

**Contraindications and Warnings/Precautions**

**Table 7. Contraindications and Warnings/Precautions1-3**

|  |  |
| --- | --- |
| **Contraindication** | Respiratory depression; oxycodone ER should not be used in patients with significant respiratory depression. |
| Acute or severe bronchial asthma; this agent should not be utilized in individuals with acute or severe bronchial asthma in an unmonitored setting. |
| Paralytic ileus and gastrointestinal obstruction; oxycodone ER should not be used in patients with known or suspected paralytic ileus or gastrointestinal obstruction. |
| Hypersensitivity; oxycodone ER should not be used in patients with known hypersensitivity (e.g., anaphylaxis) to oxycodone. |
| **Warning/ Precaution** | Addiction, abuse and misuse; although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxycodone 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 oxycodone ER, 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 oxycodone and can result in overdose and death. |
| 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 with oxycodone ER and following dose increases. |
| Neonatal opioid withdrawal syndrome; Prolonged use of oxycodone ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, 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. |
| Interactions with central nervous system depressants; Hypotension and severe sedation, coma, or respiratory depression may result if oxycodone ER is used concomitantly with other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). In addition, the patient’s use of alcohol or illicit drugs that can cause CNS depression should be evaluated. If the decision to begin oxycodone ER therapy is made, the dosage of oxycodone ER should be reduced by one-third to one-half the usual dose. Patients should be monitored for signs of sedation and respiratory depression and consideration should also be given to using a lower dose of the concomitant CNS depressant. |
| Elderly, cachetic 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 oxycodone as well as when this agent is given concomitantly with CNS depressants. |
| 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 non-opioid analgesics in these patients if possible. |
| Hypotensive effects; oxycodone 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). |
| Patients with head injury or increased intracranial pressure; monitor patients taking oxycodone 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. Oxycodone ER may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Avoid the use of oxycodone ER in patients with impaired consciousness or coma. |
| 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 oxycodone 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.  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. |
| Patients with convulsive or seizure disorders; The oxycodone in oxycodone ER may exacerbate seizures in patients with seizure disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during therapy. |
| 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 oxycodone ER as these agents can reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing oxycodone ER, gradually taper the dose. Do not abruptly discontinue medication. |
| Driving and operating machinery; oxycodone ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery until they know how they will react to the medication. |
| Cytochrome P450 3A4 inhibitors and inducers; medications that are inhibitors of CYP 3A4 may increase plasma concentrations of oxycodone and prolong opioid effects. Those that are inducers of CYP 3A4 may cause increased clearance of oxycodone which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration is necessary, individuals should be monitored at frequent intervals and dose adjustments may be necessary. |
| Laboratory monitoring; not every urine drug test for “opioids” or “opiates” detects oxycodone reliably, especially those designed for in-office use. In addition, many laboratories will report urine drug concentrations below a specified “cut-off” value as “negative”. Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results. |

**Adverse Drug Events**

**Table 8.** **Most Common Adverse Reactions (>5%) Reported by Patients in Clinical Trials Comparing OxyContin® (oxycodone ER)** **with Placebo**1-3

| **Adverse Event** | **Reported Frequency** | |
| --- | --- | --- |
| **oxycodone**  **n (%), N=227** | **Placebo**  **n (%), N=45** |
| Asthenia | 6 | - |
| Constipation | 23 | 7 |
| Dizziness | 13 | 9 |
| Dry mouth | 6 | 2 |
| Headache | 7 | 7 |
| Nausea | 23 | 11 |
| Pruritus | 13 | 2 |
| Somnolence | 23 | 4 |
| Sweating | 5 | 2 |
| Vomiting | 12 | 7 |

**Table 9. Incidence of Adverse Reactions Reported in ≥ 5 % of Patients 11 to 16 Years of Age1-3**

| **Adverse Event** | **Reported Frequency** |
| --- | --- |
| **11 to 16 years n (%), N=140** |
| Any adverse event | 71 (51) |
| Constipation | 13 (9) |
| Decreased appetite | 7 (5) |
| Diarrhea | 8 (6) |
| Dizziness | 12 (9) |
| Headache | 20 (14) |
| Nausea | 21 (15) |
| Pruritus | 8 (6) |
| Pyrexia | 15 (11) |
| Vomiting | 30 |

*Postmarketing experience:*

The following adverse reactions have been identified during post-approval use of OxyContin® (oxycodone ER): abuse, addiction, aggression, amenorrhea, cholestasis, completed suicide, death, dental caries, increased hepatic enzymes, hyperalgesia, hypogonadism, hyponatremia, ileus, intentional overdose, mood altered, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, suicidal attempt, suicidal ideation, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.1-3

Anaphylaxis has been reported with ingredients contained in OxyContin® (oxycodone ER). In addition, the following have also been reported, potentially due to the swelling and hydro gelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.1-3

**Table 10. Black Box Warning for OxyContin® (oxycodone ER) 1-3**

| **WARNING** |
| --- |
| Addiction, Abuse, and Misuse  OxyContin® (oxycodone 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 and monitor all patients regularly for the development of these behaviors or conditions.   Life-Threatening Respiratory Depression  Serious, life-threatening, or fatal respiratory depression may occur with use of OxyContin® (oxycodone ER). Monitor for respiratory depression, especially during initiation or following a dose increase. Instruct patients to swallow tablets whole; crushing, chewing, or dissolving OxyContin® (oxycodone ER) tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone.  Accidental Ingestion  Accidental ingestion of even one dose of OxyContin® (oxycodone ER), especially by children, can result in a fatal overdose of oxycodone.  Neonatal Opioid Withdrawal Syndrome  Prolonged use of OxyContin® (oxycodone 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.  Cytochrome P450 3A4 Interaction  The concomitant use of OxyContin® (oxycodone ER) with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OxyContin® (oxycodone ER) and any CYP3A4 inhibitor or inducer. |

**Drug Interactions**

There are no reported drug-food interactions with OxyContin® (oxycodone ER). However, the concurrent use of this agent and ethanol may result in an increase in CNS or respiratory depression.

**Table 11. Drug Interactions1-3**

| **Interacting Medication or Disease** | **Interaction Severity Rating\*** | **Potential Result** |
| --- | --- | --- |
| Naltrexone | Contraindicated | Concurrent use of naltrexone with selected opioids may result in precipitation of opioid withdrawal symptoms and decreased opioid effectiveness. |
| Mixed agonist/antagonist and partial agonist opioid analgesics | Major | Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of oxycodone ER or precipitate withdrawal symptoms. Avoid concurrent use. |
| CNS Depressants | Major | Concomitant use of oxycodone ER and CNS depressants such as sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, alcohol and other opioids can increase the risk of respiratory depression, profound sedation, coma or death. When combined therapy is deemed necessary, individuals should be monitored closely and the dose of one or both agents should be reduced. |
| Muscle relaxants | Major | Oxycodone ER may enhance the neuromuscular blocking action of true skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving concurrent muscle relaxants and opioids for signs of respiratory depression that may be greater than otherwise expected. |
| CYP3A4 and 2D6 inhibitors | Major | Drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone ER which could lead to an increase in oxycodone plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of CYP2D6 and 3A4 inhibitors. If co-administration with oxycodone ER is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved. |
| CYP3A4 inducers | Major | 3A4 inducers may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration with oxycodone ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved. |
| Anticholinergics | Major | Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when oxycodone ER is used concurrently with anticholinergic drugs. |
| Telithromycin | Major | Concurrent use of oxycodone ER and telithromycin may result in decreased oxycodone clearance and risk of respiratory depression. |
| Itraconazole | Major | Concurrent use of itraconazole and oxycodone ER may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Clarithromycin | Major | Concurrent use of clarithromycin and oxycodone ER may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Fluvoxamine | Major | Concurrent use of fluvoxamine and oxycodone may result in an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus and mental status changes). |
| Sertraline | Major | Concurrent use of sertraline and oxycodone may result in an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus and mental status changes). |
| Amprenavir | Major | Concurrent use of amprenavir and oxycodone may result in increased oxycodone plasma concentrations. |
| Abiraterone | Major | Concurrent use of abiraterone and oxycodone may result in increased oxycodone plasma concentrations. |
| Nefazodone | Major | Concurrent use of nefazodone and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Cobicistat | Major | Concurrent use of cobicistat and oxycodone may result in increased oxycodone plasma concentrations. |
| Amiodarone | Major | Concurrent use of amiodarone and oxycodone may result in increased oxycodone plasma concentrations. |
| Indinavir | Major | Concurrent use of indinavir and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Atazanavir | Major | Concurrent use of atazanavir and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Ketoconazole | Major | Concurrent use of ketoconazole and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Aprepitant | Major | Concurrent use of aprepitant and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Saquinavir | Major | Concurrent use of saquinavir and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Darunavir | Major | Concurrent use of darunavir and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Ritonavir | Major | Concurrent use of ritonavir and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| Diuretics | Moderate | Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Opioids may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates. |
| Econazole, Fluconazole, Miconazole and Voriconazole | Moderate | Concurrent use of miconazole and oxycodone may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |
| St John’s Wort | Moderate | Concurrent use may result in decreased plasma levels and efficacy of oxycodone. |
| Rifampin | Moderate | Concurrent use may result in decreased oxycodone exposure and plasma concentrations. |
| Ginseng | Moderate | Concurrent use may result in reduced opioid analgesic effectiveness. |
| Carbamazepine | Moderate | Concurrent use may result in decreased oxycodone exposure and plasma concentrations. |
| Phenytoin | Moderate | Concurrent use may result in decreased oxycodone exposure and plasma concentrations. |
| Azithromycin, Erythromycin | Moderate | Concurrent use may result in increased oxycodone plasma concentrations and decreased oxycodone clearance. |

\*Severity rating per Micromedex

**Patient Monitoring Guidelines3**

Before starting therapy with an opioid, individuals should be evaluated for potential signs of addiction, abuse or misuse of medications. If started, they should continue to be monitored frequently for any changes in behavior. While the individual is receiving opioid analgesics they should be monitored for adequacy of analgesia as well as continually assessed for the need of continued opioid treatment.

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

* respiratory depression and sedation; especially within 24 to 72 hours 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
* 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

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