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 C_{max} when compared to immediate-release (IR) oxycodone and that the median T_{max} 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 Availability[59]

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 via smoking. 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 C_{max} and increased T_{max} 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) E_{max} values were significantly lower ($P \leq 0.05$) 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