**OxyContin® (oxycodone HCl) extended-release tablets**

**Formulary Submission Dossier**

## Prepared for:

### Tyson Thompson, PharmD Massachusetts Drug Formulary Commission

*In accordance with the Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions (Version 3.1)*

## V3.1 Prepared by:

### Medical Services Department Purdue Pharma L.P. One Stamford Forum

Stamford, CT 06901-3431

(888) 726-7535, option #1

**The enclosed Document is provided to the above stated recipient in response to an unsolicited request for this information. This Document is provided with the understanding that the Document contains the confidential and proprietary information of Purdue Pharma L.P. (“Purdue”). Purdue reserves all rights to the Document and all confidential and proprietary information contained in the Document. Any review, disclosure or publication, in whole or part, of any information contained in this Document that is not specifically authorized in writing by an authorized representative of Purdue is strictly prohibited and would constitute a violation of the rights of Purdue.**

#### WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

**Addiction, Abuse, and Misuse**

**OxyContin® 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 OxyContin and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)].***

**Life-Threatening Respiratory Depression**

**Serious, life-threatening, or fatal respiratory depression may occur with use of OxyContin. Monitor for respiratory depression, especially during initiation of OxyContin or following a dose increase*.* Instruct patients to swallow OxyContin tablets whole; crushing, chewing, or dissolving OxyContin tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.2)]*.**

**Accidental Ingestion**

**Accidental ingestion of even one dose of OxyContin, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.2)]*.**

#### Neonatal Opioid Withdrawal Syndrome

**Prolonged use of OxyContin 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 *[see Warnings and Precautions (5.3)]*.**

**Cytochrome P450 3A4 Interaction**

**The concomitant use of OxyContin 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 and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.14) and Clinical Pharmacology (12.3)]*.**

**TABLE OF CONTENTS**

[TABLE OF CONTENTS 1](#_bookmark0)

1. [EXECUTIVE SUMMARY – CLINICAL AND ECONOMIC VALUE OF THE PRODUCT 3](#_bookmark1)
   1. [*Clinical Benefits 3*](#_bookmark2)
   2. [*Economic Benefits 4*](#_bookmark3)
   3. [*Conclusions 5*](#_bookmark4)
2. [PRODUCT INFORMATION AND DISEASE DESCRIPTION 7](#_bookmark5)
   1. [*Product Description 7*](#_bookmark6)
   2. [*Place of the Product in Therapy 41*](#_bookmark7)
3. [SUPPORTING CLINICAL EVIDENCE 62](#_bookmark9)
   1. [*Summarizing Key Clinical Studies 62*](#_bookmark10)
      1. [*Published and Unpublished Data and Clinical Studies Supporting Labeled Indications 62*](#_bookmark12)
      2. [*Published and Unpublished Data and Clinical Studies Supporting Off-Label Indications 117*](#_bookmark30)
      3. [*Clinical Evidence Table Spreadsheets of all Published and Unpublished Studies 120*](#_bookmark31)
      4. [*Summary of Evidence from Secondary Sources 151*](#_bookmark32)
4. [ECONOMIC VALUE AND MODELING REPORT 154](#_bookmark33)
5. [OTHER SUPPORTING EVIDENCE 155](#_bookmark34)
   1. [*Summarizing Other Relevant Evidence 155*](#_bookmark35)
      1. [*Published and Unpublished Studies Supporting Labeled and Off-Label Indications 155*](#_bookmark36)
      2. [*Evidence Table Spreadsheets of all Published and Unpublished Studies 181*](#_bookmark40)
6. [SUPPORTING INFORMATION 185](#_bookmark41)
   1. [*References Contained in Dossier 185*](#_bookmark42)

**1. EXECUTIVE SUMMARY – CLINICAL AND ECONOMIC VALUE OF THE PRODUCT**

* 1. **linical Benefits**

OxyContin is an extended-release oral formulation of oxycodone hydrochloride 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; 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. OxyContin is designed to provide delivery of oxycodone over 12 hours. OxyContin Tablets were reformulated in 2010 in an effort to make the tablet more difficult to manipulate for the purpose of intentional misuse and abuse or inadvertent medication error. Reformulated OxyContin has physicochemical barriers to crushing, dissolving and breaking – manipulations often required or preferred for abuse through intravenous and intranasal routes.

More than 2,000 adult patients have been enrolled in OxyContin 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. The accumulated clinical efficacy and safety data for OxyContin tablets are summarized below.

* + - A consistent pattern of pain reduction or continuing, stable pain control supported the analgesic efficacy of OxyContin across all studies involving patients with cancer- and noncancer-related pain syndromes, including pain associated with conditions such as osteoarthritis and postoperative pain.
    - In controlled studies, OxyContin tablets were superior to placebo and as effective as immediate-release (IR) oxycodone tablets, fixed combination oxycodone and acetaminophen (APAP) tablets, or MS Contin (morphine sulfate extended-release tablets) for reducing pain intensity ([Kaplan](#_bookmark14) et al. 1998; [Mucci-](#_bookmark13)  [LoRusso](#_bookmark13) et al. 1998; [Citron](#_bookmark15) et al. 1998; [Caldwell](#_bookmark18) et al. 1999; [Hale](#_bookmark19) et al. 1999; [Nicholson](#_bookmark29) et al. 2006).
    - Among patients with osteoarthritis-related pain, use of OxyContin was associated with significant improvements, compared to placebo, in patient-reported outcomes in the areas of pain, stiffness, and function as assessed by the Western Ontario and McMaster Universities Arthritis Index (WOMAC), significant decreases in pain intensity and interference of pain with daily activities, and significant improvements in quality of sleep ([Markenson](#_bookmark16) et al. 2005).
    - Among patients with post-herpetic neuralgia, use of OxyContin was associated with significant reductions, compared to placebo, in pain intensity and disability scores (physician rating) and increased pain relief, global effectiveness (patient rating), and patient preference ([Watson](#_bookmark23) et al. 1998).
    - Two controlled studies and an open-label study in patients with painful diabetic neuropathy demonstrated OxyContin’s efficacy in treating moderate to severe pain due to diabetic neuropathy by decreasing pain intensity ([Yao](#_bookmark20) et al. 2012; [Gimbel](#_bookmark21) et al. 2003; [Watson](#_bookmark22) et al. 2003).
    - Among patients having undergone total knee arthroplasty, use of scheduled OxyContin (+IR oxycodone as needed) vs. placebo (+IR oxycodone as needed) was associated with significant improvements in pain, physical functioning, and an average 2.3 day reduction in inpatient rehabilitation stay ([Cheville](#_bookmark27) et al. 2001).
    - Long-term trials have demonstrated the effectiveness of OxyContin in the management of chronic noncancer pain, including an open-label, registry trial with up to 3 years of follow-up ([Portenoy](#_bookmark28) et al. 2007) and an open-label, extension trial with a duration of OxyContin exposure for up to 18 months ([Roth](#_bookmark17) et al. 2000).
    - In pre-marketing, open-label trials in patients with cancer pain, the average total daily dose of OxyContin was 105 mg (range, 20 mg to 640 mg/day).
    - OxyContin tablets were safely used with a variety of non-opioid analgesics, analgesic adjuvants, and other concomitant drugs.
    - The adverse event profile of OxyContin is consistent with that of other approved opioid analgesics. The safety of OxyConitn was evaluated in double-blind clinical trials involving 713 patients with moderate to

Clinical studies conducted with original OxyContin Tablets formulation

severe pain of various etiologies. The most common adverse reactions (>5%) reported by patients in clinical trials were constipation, nausea, somnolence, dizziness, pruritus, vomiting, headache, dry mouth, asthenia, and sweating. Serious side effects of OxyContin include respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock. There is a potential for drug addiction to develop following exposure to opioids even under appropriate medical use. All patients treated with opioids require careful monitoring for signs of misuse, abuse, and addiction.

Furthermore, the safety and efficacy of OxyContin have been established in pediatric patients ages 11 to 16 years (OTR3001). OxyContin was evaluated in an open-label clinical trial of 155 opioid-tolerant pediatric patients ages 6 to 16 with moderate to severe chronic pain where:

* The mean duration of therapy was 20.7 days (range 1 to 43 days).
* The starting total daily doses ranged from 20 mg 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).
* Overall, OxyContin, alone or in combination with supplemental analgesics, reduced or maintained pain right now scores from baseline to week 4.
* Too few patients less than 11 years 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.

While fixed combination oxycodone products containing aspirin (ASA) or APAP are effective for the management of moderate to moderately severe pain, the dose and duration of such products is limited by certain toxicities of the non-opioid analgesic component. APAP use has been associated with hepatic and renal damage after chronic use at therapeutic dosages or when excessive amounts (>4 g/day) are taken over a short period of time. In addition, non-steroidal anti-inflammatory drugs (NSAIDs), such as ASA or ibuprofen, have associated toxicities that include bleeding, gastric ulceration and renal failure. OxyContin is a single- entity opioid and, therefore, contains no ASA, APAP, or NSAIDs. There is no maximum daily dose limit for OxyContin, the ceiling to its analgesic effectiveness is limited only by adverse reactions This is not true of the mixed agonist-antagonist opioid and non-opioid analgesics that have a ceiling to analgesia.

While oxycodone and morphine demonstrate similar safety and efficacy in relieving pain, there are distinguishing features between these two drug substances that include potency, histamine release, side-effect profiles, metabolites, pharmacokinetic profiles, as well as their delivery systems. The treating clinician needs to take such differences into account based on the individual patient situation.

For patients with continuous chronic pain, compliance with administration of analgesics is essential to prevent gaps in pain relief. These patients may benefit from an extended-release or long-acting analgesic with every 12-hour dosing. Although there is no evidence of superiority of long-acting over immediate-release formulations, some pain management guidelines recommend the use of long-acting agents in appropriate patients with chronic pain (Veterans Health Administration, Department of Defense [VA/DoD] 2010). Every 12- hour dosing with OxyContin decreases pill burden, may decrease the need to awaken at night to take another

dose of pain medication, may cause less clock-watching by the patient in chronic pain, and, of course, provides a simplified dosing regimen for the patient.

## Economic Benefits

Chronic pain has a profound impact on all areas of patients‘ lives and has a huge economic burden on society (Porreca et al. 2006). Chronic pain adversely affects quality of life, including job performance, social relationships, normal daily activities, and emotional well-being (McCarberg et al. 2008). In a survey of working adults, it was determined that lost productive time (due to absenteeism and to reduced performance while at work or ―presenteeism) from pain due to conditions such as headache, arthritis, back pain and other musculoskeletal conditions costs an estimated $61.2 billion per year. The majority (76.6%) of lost productive time was explained by reduced work performance, not absenteeism (Stewart et al. 2003). Another study

evaluating arthritis pain exacerbations in U.S. workers found that the estimated lost productive work time from arthritis in the U.S. workforce was $7.11 billion, with 65.7% of this cost attributed to the 38% of workers with pain exacerbations (Ricci et al. 2005).

Direct medical costs from uncontrolled pain are attributed to more frequent medical service utilization, including physician office visits, emergency department visits, and unscheduled hospitalizations (Grant et al. 1995).

Costs of uncontrolled pain also include impairments in health-related quality of life (HRQL) such as decreased sleep, decreased physical functioning, decreased enjoyment of life, decreased ability to perform normal work, and decreased activity (Galer et al. 2000; Briggs et al. 1999).

Although limited, data on the financial impact of OxyContin suggest that OxyContin is cost-effective and that its use is associated with decreased healthcare utilization (see [Section 5.1](#_bookmark35)). The use of OxyContin was associated with an average 2.3 day reduction in inpatient services among patients following total knee arthroplasty ([Cheville](#_bookmark27) et al. 2001). A retrospective database study demonstrated OxyContin to have economic advantages by showing that health-care costs were $17,580 higher among patients who switched therapy versus those who did not. The study documented that patients who begin therapy with controlled-release oxycodone are less likely to switch to another medication than those initially treated with either transdermal fentanyl or controlled-release morphine. These findings are of economic relevance, as health-care costs are significantly higher among patients who switch long-acting opioid analgesic therapy in comparison with those who do not ([Berger](#_bookmark39) et al. 2004).

In 2007, the total costs of prescription opioid abuse were estimated at $55.7 billion, including $25.6 billion for lost productivity, $25.0 billion for health care, and $5.1 billion for criminal justice costs (Birnbaum 2011).

Studies of the Veterans Health Administration, Medicaid, and commercial insurers have also demonstrated significantly higher healthcare utilization and costs for those who abuse opioids, versus those who do not (Baser et al. 2014; Rice et al. 2013; McAdam-Marx et al. 2010; White et al. 2005). Opioids with abuse- deterrent technology have the potential to reduce costs associated with abuse and dependence. Using data from the Truven Health Analytics database from 2009 through 2011, it has been estimated that use of reformulated extended-release oxycodone would result in a savings of $430 million (2011 dollars) in medical and drug costs among diagnosed and undiagnosed abusers ([Rossiter](#_bookmark37) et al. 2014). An extension of this analysis, which assumed that reformulated extended-release oxycodone would affect both direct and indirect costs to the same extent, estimated a total savings of approximately $1 billion (2011 dollars), with reductions in criminal justice costs, lost productivity, and medical and drug costs for caregivers making up the additional

$605 million in savings ([Kirson](#_bookmark38) et al. 2014).

## nclusions

In summary, a consistent pattern of pain reduction or continuing, stable pain control supported the analgesic efficacy of OxyContin among patients with chronic malignant and non-malignant pain syndromes. Use of OxyContin has been associated with significant improvements in patient-reported outcomes and available economic evidence suggests that OxyContin represents a cost-effective use of scarce health resources (see [Section 5.1](#_bookmark35)).

Additionally, the development of opioid formulations that have abuse-deterrent properties is of significant importance in providing a societal benefit in helping to curtail the serious public health problem of opioid drug abuse and misuse, while continuing to allow access for patients who require opioid analgesics.

OxyContin, as an extended-release oral formulation of single-entity oxycodone, helps to fill the unmet need for safe and effective therapies to treat chronic pain in adults as well as opioid-tolerant pediatric patients 11 years of age or older. OxyContin has abuse-deterrent properties that have resulted in 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. Clinical studies have also demonstrated a consistent pattern of pain reduction or continuing maintenance of pain control in patients with chronic pain. Furthermore,

as a single-entity oxycodone formulation, OxyContin is not subject to the potential toxicities of non-opioid components, such as acetaminophen, when taken at doses exceeding the maximum recommended dose.

**2. PRODUCT INFORMATION AND DISEASE DESCRIPTION**

## Product Description

* + 1. **Generic Name, Brand Name, and Therapeutic Class**

Brand Name: OxyContin®

Generic Name: oxycodone hydrochloride extended-release tablets Therapeutic Class: opioid analgesic

## 2.1.b.-2.1.d. Dosage form, Strength, Package Size, NDC Number, and WAC

#### Table 1. OxyContin Tablets Description, How Supplied, NDC Number, and WAC

|  |  |  |  |
| --- | --- | --- | --- |
| **Product Description** | **How Supplied** | **NDC Number** | **WAC ($)** |
| OxyContin (oxycodone hydrochloride) extended- release tablets 10 mg are round, white-colored, bi- convex tablets debossed with OP on one side and 10 on the other | Child-resistant closure, opaque plastic bottles of 100 | 59011-410-10 | 279.94 |
| Unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton | 59011-410-20 | 57.48 |
| OxyContin (oxycodone hydrochloride) extended - release tablets 15 mg are round, gray-colored, bi- convex tablets debossed with OP on one side and 15 on the other | Child-resistant closure, opaque plastic bottles of 100 | 59011-415-10 | 412.13 |
| Unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton | 59011-415-20 | 84.55 |
| OxyContin (oxycodone hydrochloride) extended - release tablets 20 mg are round, pink-colored, bi- convex tablets debossed with OP on one side and 20 on the other | Child-resistant closure, opaque plastic bottles of 100 | 59011-420-10 | 522.07 |
| Unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton | 59011-420-20 | 107.09 |
| OxyContin (oxycodone hydrochloride) extended - release tablets 30 mg are round, brown-colored, bi- convex tablets debossed with OP on one side and 30 on the other | Child-resistant closure, opaque plastic bottles of 100 | 59011-430-10 | 726.08 |
| Unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton | 59011-430-20 | 148.97 |
| OxyContin (oxycodone hydrochloride) extended - release tablets 40 mg are round, yellow-colored, bi- convex tablets debossed with OP on one side and 40 on the other | Child-resistant closure, opaque plastic bottles of 100 | 59011-440-10 | 894.11 |
| Unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton | 59011-440-20 | 183.33 |
| OxyContin (oxycodone hydrochloride) extended - release tablets 60 mg are round, red-colored, bi- convex tablets debossed with OP on one side and 60 on the other | Child-resistant closure, opaque plastic bottles of 100 | 59011-460-10 | 1,265.91 |
| Unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton | 59011-460-20 | 259.72 |
| OxyContin (oxycodone hydrochloride) extended - release tablets 80 mg are round, green-colored, bi- convex tablets debossed with OP on one side and 80 on the other | Child-resistant closure, opaque plastic bottles of 100 | 59011-480-10 | 1,560.19 |
| Unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton | 59011-480-20 | 320.05 |

**OxyContin Delivery System**

OxyContin tablets are designed to provide oxycodone delivery over a 12-hour period of time, allowing for every-12-hour dosing.

OxyContin utilizes a matrix drug delivery system with a colored, cosmetic, film coat. This cosmetic coat does not affect drug delivery – its only purpose is to differentiate tablet strengths (Data on File). In matrix-type drug delivery systems, the active pharmaceutical ingredient and ingredient(s) that control the rate of release of the active ingredient (retardant(s)) are uniformly distributed throughout the dosage form (Langer, 1993). OxyContin tablets do not contain an immediate-release component nor do they behave pharmacokinetically as though they do. Oxycodone release from OxyContin is independent of surrounding pH.

Dose dumping is the unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified-release dosage form (Langer, 1993). Dose dumping does not occur when OxyContin Tablets are taken as directed (Data on File).

OxyContin is formulated with RESISTEC™ technology. RESISTEC is Purdue Pharma’s proprietary extended- release solid oral dosage formulation platform. 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 (Data on File).

##### *Abuse-deterrent Technology*

The physicochemical attributes of OxyContin 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. OxyContin has physicochemical properties that confer resistance to crushing, dissolving and breaking – manipulations often required or preferred for abuse through intravenous and intranasal routes, and it maintains some extended-release characteristics even if the tablet is physically compromised.

In addition to tablet size and shape, the rate of release of oxycodone from each OxyContin 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. After treatment via a specific manufacturing process, it is also the polyethylene oxide excipient that imparts hardness to the tablet (Data on File).

This technology is not expected to have an impact on the ability for nonmedical use by swallowing a single or multiple intact tablets. It should be noted that not all opioid formulations that incorporate abuse-deterrent technologies possess equivalent degrees of abuse deterrence; a comprehensive *in vitro* and *in vivo* research program is required to determine if a given product meets FDA standards for abuse-deterrent properties.

Subsection 9.2, Abuse, of the [OxyContin Full Prescribing Information](http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o) describes results from abuse-deterrence studies, summarizes them, and specifies certain abuse-deterrent properties (labeling claims) of OxyContin.

OxyContin 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 (FDA 2015). However, abuse of OxyContin by the intravenous, intranasal, and oral routes is still possible.

Abuse of OxyContin poses a risk of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of OxyContin with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved OxyContin enhances drug release and increases the risk of overdose and death. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

With parenteral abuse, the inactive ingredients in OxyContin can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

## AHFS Classification

Opiate Agonists: 28:08.08

## FDA-approved Indications

OxyContin 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, FDA approved a supplemental NDA (sNDA) for the OxyContin Full Prescribing Information to include labeling for a pediatric indication in opioid-tolerant pediatric patients 11 years of age and older. As a result, OxyContin is 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.

*Limitations of Use*

* + - * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OxyContin for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
      * OxyContin is not indicated as an as-needed (prn) analgesic

**Date of Approval:** Original OxyContin Tablets were approved for marketing in December 1995. Reformulated OxyContin Tablets were approved April 5, 2010. In August 2010, Purdue stopped shipping the original OxyContin formulation and began exclusively shipping reformulated OxyContin. On April 18, 2013, FDA published notice of its determination that original OxyContin, NDA 20–553, was withdrawn from sale for reasons of safety or effectiveness (78 FR 23273).

Purdue elected to reformulate OxyContin Tablets in an effort to make the tablet more difficult to manipulate for the purpose of intentional abuse by various routes of administration (eg, snorting and intravenous injection) or misuse by inadvertent medication error (eg, crushing or cutting a tablet). Reformulated OxyContin is considered therapeutically equivalent to the original formulation, by virtue of meeting the FDA criteria for bioequivalence to the original formulation.

Prior to the approval of the reformulation by FDA in April 2010, a comprehensive evaluation of the tablet’s physicochemical properties and potential to deter abuse was conducted. These experiments, designed by experts in methods of abuse and chemical extraction, demonstrated that defeating the reformulated tablet’s controlled-release properties requires more time and effort than for the original OxyContin formulation. (Cone et al. 2012; Cone et al. 2013)

Additionally, the impact of these properties on abuse potential was evaluated in multiple human pharmacokinetic and abuse potential studies. The results from these studies indicate that reformulated OxyContin should be less attractive as a drug of abuse when the method of abuse requires the tablet to be manipulated (Harris et al. 2012; Perrino et al. 2012; Sellers et al. 2012)

## Pharmacology

Please refer to section 12 of the [Full Prescribing Information](http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o) for clinical pharmacology.

The precise mechanism of analgesic action of oxycodone is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spina l cord and play a role in the analgesic effects of this drug. Opioid analgesics can be categorized by their pharmacologic activity at specific opioid receptor(s). Mu (µ), delta (δ), and kappa (κ) are the three major opioid receptor classes that mediate analgesia and the other effects of opioid analgesics. The mu-opioid receptor is the prototypic opioid receptor and remains the most important in the clinical management of pain (Cherny et al. 1996; Reisine and Pasternack, 1996; Gourlay et al. 2005; Inturrisi et al. 2002; Pasternak et al. 2004). Morphine and morphine-like compounds, such as oxycodone, are opioid agonists that produce analgesia primarily through interaction with -opioid receptors. Agonism at the -opioid-receptor is associated with effects such as analgesia, respiratory depression, sedation, miosis, euphoria, and reduced gastrointestinal motility (Cherny et al. 1996; Reisine and Pasternack, 1996; Gourlay et al. 2005).

## Pharmacokinetics/Pharmacodynamics

Please refer to sections 12.2 and 12.3 of the [Full Prescribing Information](http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o) for pharmacodynamics and pharmacokinetics, respectively.

#### Dose Proportionality

Dose proportionality has been established for OxyContin 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (maximum concentration [Cmax]) and extent of absorption as determined by the Area Under the time-plasma concentration Curve (AUCinf) (see **Table 2**).

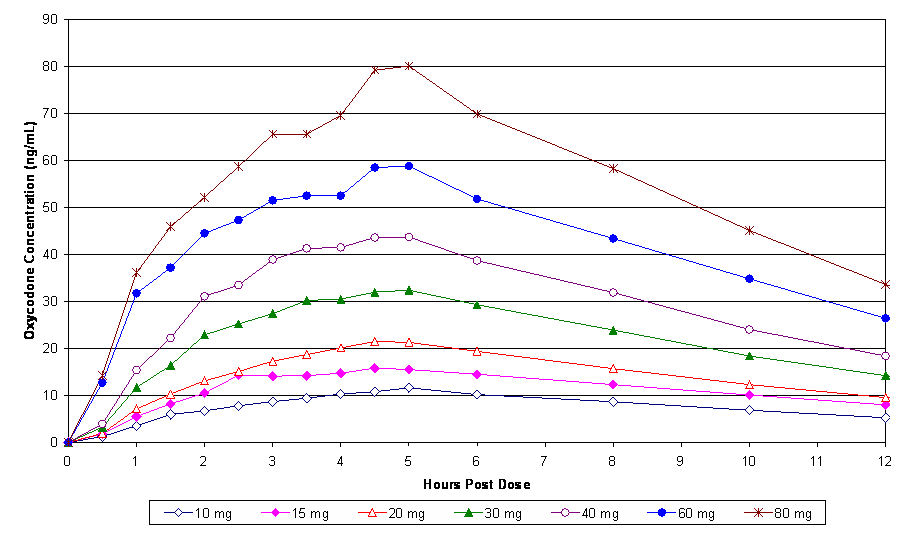
#### Table 2. Mean [% coefficient of variation] Pharmacokinetic Values

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Regimen** | **Tablet Strength** | **AUC0-inf**  (ng•hr/mL) | **Cmax**  (ng/mL) | **Tmax**  (hr) |
| Single Dose† | 10 mg | 136 [ +27%] | 11.5 [ +27%] | 5.11 [ +21%] |
|  | 15 mg | 196 [ +28%] | 16.8 [ +29%] | 4.59 [ +19%] |
|  | 20 mg | 248 [ +25%] | 22.7 [ +25%] | 4.63 [ +22%] |
|  | 30 mg | 377 [ +24%] | 34.6 [ +21%] | 4.61 [ +19%] |
|  | 40 mg | 497 [ +27%] | 47.4 [ +30%] | 4.40 [ +22%] |
|  | 60 mg | 705 [ +22%] | 64.6 [ +24%] | 4.15 [ +26%] |
|  | 80 mg | 908 [ +21%] | 87.1 [ +29%] | 4.27 [ +26%] |
| †data obtained while subjects received naltrexone, which can enhance absorption | | | | |

Dose proportionality of OxyContin was evaluated in two separate studies, one assessing 10 mg to 40 mg tablets and the other assessing 40 mg to 80 mg tablets. Each of the studies was a randomized, open-label, single-dose, crossover design in healthy, opioid-naïve adult subjects dosed in the fasted state. A minimum washout of six days separated dose administrations, and blood samples were obtained pre-dose and at additional time points through 72 hours post-dose (see **Figure 1**) (Data on File).

The 90% confidence intervals associated with dose-proportionality slope estimates for Cmax and AUC were entirely contained within the defined critical ranges for the 10 mg to 40 mg and the 40 mg to 80 mg dosage ranges, demonstrating dose proportionality across the 10 mg to 80 mg dosage strengths (see **Table 3**) (Data on File).

#### Figure 1. Plasma Oxycodone Concentrations Following Single Doses of OxyContin Tablets



**Table 3. Dose Proportionality Statistical Results Across Studies**

a90% confidence interval (CI) of dose normalized to 10 mg.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Doses** | **Pharmacokinetic Parameters** | **Slope Estimate** | **90% Confidence Intervala** | **Critical Rangeb** |
| 10 mg – 40 mg | Cmax (ng/mL) | 1.06 | [1.03 - 1.09] | [0.839 - 1.1610] |
|  | AUC0-inf (ng•hr/mL) | 0.959 | [0.935 - 0.982] |  |
| 40 mg – 80 mg | Cmax (ng/mL) | 0.845 | [0.771 - 0.919] | [0.6781 - 1.3219] |
|  | AUC0-inf (ng•hr/mL) | 0.967 | [0.910 - 1.03] |  |

bA mixed model was used to estimate the slope and its associated 90% confidence interval. Dose proportionality was achieved when the 90% CI lies entirely within the critical range determined from the acceptance interval for the ratio of dose-normalized geometric mean values and the maximal dose ratio used in the study (Smith BP et al. 2000).

#### Bioequivalence

While the pharmacokinetic profiles for reformulated and original OxyContin Tablets are not exactly the same, the reformulation has met strict FDA bioequivalence criteria compared to the original formulation, which means there is no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient.

Mean values for AUC0-inf, Cmax, and time required to reach peak plasma concentration (Tmax) for reformulated OxyContin are provided in **Table 2**. The mean Tmax values for reformulated OxyContin following single-dose administrations are longer than original OxyContin. Mean Tmax values for original OxyContin following single- dose administrations ranged from 2.1 to 3.2 hours (Benziger et al, 1995; Data on File).

Bioequivalence of reformulated OxyContin to original OxyContin Tablets was evaluated in six randomized, open-label, single-dose, two-way crossover studies in healthy, opioid-naïve adult subjects. In the fed and fasted states, bioequivalence has been established between reformulated OxyContin Tablets and the original OxyContin formulation for the 10 mg, 40 mg and 80 mg tablet strengths (see **Table 4**) (Data on File).

#### Table 4. Pharmacokinetic Results in the Fed and Fasted States of Bioequivalence Studies

aMixed-model analysis of variance used to compared (test vs. reference) logarithmic-transformed values from test and reference treatments.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **OxyContin Dose** | **Condition** | **Cma** a  **x** | | **AUCin** a  **f** | |
| **LS Mean Ratio**b | **90% Confidence Interval**c | **LS Mean Ratio**b | **90% Confidence Interval**c |
| 10 mg | Fed | 105 | [101.06 - 108.51] | 95.6 | [93.73 - 97.53] |
| Fasted | 102 | [99.35 - 105.42] | 98.0 | [94.94 - 101.19] |
| 40 mg | Fed | 99.9 | [95.40 - 104.52] | 92.6 | [90.11 - 95.09] |
| Fasted | 96.6 | [92.80 - 100.56] | 94.8 | [92.42 - 97.24] |
| 80 mg | Fed | 110 | [105.21 - 114.47] | 94.7 | [92.71 - 96.64] |
| Fasted | 103 | [98.67 - 106.66] | 97.0 | [94.20 - 99.81] |

bRatio% (test mean/reference mean) of least square means (ANOVA) derived from logarithmic-transformed values of AUC and Cmax. c90% confidence interval (CI) of the ratio

Mean oxycodone plasma concentration time curves plotted over a 12-hour and 72-hour period from the bioequivalence studies are shown below. **Figure 2** and **Figure 3** depict the plasma concentration for original OxyContin and reformulated OxyContin 10 mg and 80 mg tablets, respectively, over a *12-hour* period following administration in the fasted state. **Figure 4** and **Figure 5** show the plasma concentration for original OxyContin and reformulated OxyContin 10 mg and 80 mg tablets, respectively, over a *72-hour* period following administration in the fasted state (Data on File).

#### Figure 2. Bioequivalence of Reformulated and Original Oxycontin 10 mg Tablets in Fasted State Over

***12 Hours* Post-Dose**

10

9

8

7

6

5

4

3

Original OxyContin 10 mg, Fasted (n=81)

2

Reformulated OxyContin 10 mg, Fasted (n=81)

1

0

0

1

2

3

4

5 6 7

**Time (h)**

8

9

10 11 12

**Oxycodone Concentration (ng/mL)**

#### Figure 3. Bioequivalence of Reformulated and Original Oxycontin 80 mg Tablets in Fasted State Over

***12 Hours* Post-Dose**

90

80

70

60

50

40

30

Original OxyContin 80 mg, Fasted (n=73)

20

Reformulated OxyContin 80 mg, Fasted (n=78)

10

0

0

1

2

3

4

5 6 7

**Time (h)**

8

9

10 11

12

**Oxycodone Concentration (ng/mL)**

#### Figure 4. Bioequivalence of Reformulated and Original OxyContin 10 mg Tablets in Fasted State Over

***72 Hours* Post-Dose**

Original OxyContin 10 mg, Fasted (n=81)

Reformulated OxyContin 10 mg, Fasted (n=81)

10

9

8

7

6

5

4

3

2

1

0

0

6

12 18 24

30 36 42

**Time (h)**

48 54 60 66 72

**Oxycodone Concentration (ng/mL)**

#### Figure 5. Bioequivalence of Reformulated and Original OxyContin 80 mg Tablets in Fasted State Over

***72 Hours* Post-Dose**

Original OxyContin 80 mg, Fasted (n=73)

Reformulated OxyContin 80 mg, Fasted (n=78)

90

80

70

60

50

40

30

20

10

0

0

6

12 18 24

30 36 42

**Time (h)**

48 54 60 66 72

**Oxycodone Concentration (ng/mL)**

Overall, study results demonstrate that in both the fed and fasted states the 10 mg, 40 mg, and 80 mg reformulated OxyContin Tablets are bioequivalent to the original OxyContin formulation, which means there is no significant difference in the rate and extent of absorption of the therapeutic ingredient (oxycodone) between the two formulations (Data on File).

## ntraindications, Warnings, Precautions, and Adverse Reactions

Please refer to the Boxed Warning and sections 4, 5, and 6 of the [Full Prescribing Information](http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o).

## Interactions

Please refer to section 7 of the [Full Prescribing Information](http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o) for drug interactions.

## ge and Administration

Please refer to section 2 of the [Full Prescribing Information](http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o) for dosage and administration.

## Access

OxyContin is a schedule II controlled substance approved 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; 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. It must be dispensed with the OxyContin Medication Guide.

## Co-Prescribed / Concomitant Therapies

The American Pain Society (APS) in their *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain* recommends the use of supplemental analgesia with sustained-release opioids. Patients prescribed sustained-release opioid preparations should also be provided supplementary doses of immediate-

release opioid equivalent to about 10-15% of the total 24-hour dose, to be given every 2 hours as needed (APS 2008).

According to the VA/DoD, supplemental opioids may be considered if a patient is experiencing rescue, breakthrough pain, and incident pain. If a short-acting pure agonist opioid, either alone or in combination with a non-opioid analgesic, is used for supplemental therapy, the dose should be equivalent to about 10-15% of the total 24-hour dose, the every four hourly equivalent, or 1/6th of the total 24-hour opioid dose, as needed (VA/DoD 2010).

Please see section 2.5, Titration and Maintenance of Therapy in Adults and Pediatric Patients 11 Years and Older, of the OxyContin [Full Prescribing Information](http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o). Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid or non- opioid medication. Individually titrate OxyContin to a dose that provides adequate analgesia and minimizes adverse reactions.

#### OxyContin Clinical Trials and Supplemental Opioid Analgesic Use

In several of the OxyContin clinical trials, the study protocols included provisions for supplementary analgesia. Depending on the particular study, the dosing for supplemental analgesia was 1/6 to 1/8 (12% to 16%) of the daily OxyContin dose ([Kaplan](#_bookmark14) et al. 1998; Heiskanen et al. 1997) or 1/4 to 1/3 of the every 12 hour dose of OxyContin ([Citron](#_bookmark15) et al. 1998; [Mucci-LoRusso](#_bookmark13) et al. 1998).

## OxyContin and Comparator Products (Prescribing Information)

The following tables (**Tables 5.1-5.7**) provide a comparison of selected prescribing information for OxyContin and its primary comparator opioid analgesics.

#### Tables 5.1-5.7. Comparison of OxyContin and Opioid Analgesic Products

**(Reference: Information in Tables 5.1-5.7 is obtained from each individual product’s Full Prescribing Information)**

#### Table 5.1. Comparison of OxyContin and Opioid Analgesic Products

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Product** | **Indications and Usage** | **Mechanism of Action** | **Dosing Interval and Administration** | **Titration** | **Maximum Dose** | **Food Effect** | **Alcohol Pharma- cokinetic Effect** | **Abuse- Deterrence Labeling Claims** |
| **REFERENCE DRUG:**  **OxyContin®**  **(oxycodone HCl ER), CII** | 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; 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.  Limitations of Use   * Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release formulations, reserve OxyContin for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate- release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. * OxyContin is not indicated as an as-needed (prn) analgesic. | The precise mechanism of the analgesic action is unknown. However, specific 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. | * Every 12 hours * Swallow tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxycodone * Take OxyContin one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth * OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. | * Every 1- 2 days | * Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. * Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression. | * Food has no significant effect on the extent of absorption of oxycodone from OxyContin | * No | * Yes |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Butrans® (buprenorphine) Transdermal System, CIII** | For the management of pain severe enough to require daily, around-the- clock, long-term opioid treatment for which alternative treatment options are inadequate.  Limitations of Use   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Butrans for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate- release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. * Butrans is not indicated as an as-needed (prn) analgesic | Buprenorphine is a partial agonist at mu opioid receptors.  Buprenorphine is also an antagonist at kappa opioid receptors, an agonist at delta opioid receptors, and a partial agonist at ORL-1 (nociceptin) receptors. The contributions of these actions to its analgesic profile are unclear.  Its clinical actions result from binding to the opioid receptors. | * Every 7 days * Intended for transdermal use only * Apply to the upper outer arm, upper chest, upper back or the side of the chest. Rotate among the 8 described skin sites. After Butrans removal, wait a minimum of 21 days before reapplying to the same skin site * Apply to a hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. Do not apply to irritated skin. If the application site must be cleaned, clean the site with water only. Do not use soaps, alcohol, oils, lotions, or abrasive devices. Allow the skin to dry before applying butrans. | * Every 72 hours | * The maximum Butrans dose is 20 mcg/hr * Do not exceed a dose of one 20 mcg/hr Butrans system due to the risk of QTc interval prolongation | * N/A | * No | * No |
| **Duragesic®**  **(fentanyl transdermal system), CII** | For the management of pain in opioid-tolerant patients, severe enough to require daily, around-the- clock, long-term opioid treatment and for which alternative treatment options are inadequate.  Patients considered opioid- tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.  Limitations of Use   * Because of the risks of addiction, abuse, and | Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu- receptor. These  mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. | * Every 72 hours * Intended for transdermal use only * Apply patch to intact, non‑irritated, and non- irradiated skin on a flat   surface such as the chest, back, flank, or upper arm. The next patch is applied to a different skin site after removal of the previous transdermal system.   * Avoid exposing application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, | * Every 3 days | * N/A | * N/A | * No | * No |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve Duragesic for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate- release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. |  | saunas, hot tubs, and heated water beds, while wearing the system |  |  |  |  |  |
| **Hysingla® ER**  **(hydrocodone bitartrate), CII** | 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.  Limitations of Use   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve Hysingla ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate- release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain * Hysingla ER is not indicated as an as- needed analgesic. | Hydrocodone is an orally active semi-synthetic opioid agonist derived from two naturally occurring opiates, codeine and thebaine.  Hydrocodone is a relatively selective μ- opioid receptor agonist compared to other opioids. Hydrocodone acts as an agonist binding to and activating opioid receptors in the brain and spinal cord, which are coupled to G- protein complexes and modulate synaptic transmission through adenylate cyclase. The pharmacological effects of hydrocodone including analgesia, euphoria, respiratory depression and physiological dependence are believed to be primarily mediated via μ opioid receptors. | * Every 24 hours * Daily doses of Hysingla ER greater than 80 mg are only for use in opioid tolerant patients * Hysingla ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Crushing, chewing, or dissolving Hysingla ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death | * Every 3-   5 days | * N/A | * Can be administered without regard to food * Cmax was higher (54%) under high fat conditions relative to fasting conditions; however, AUC of Hysingla ER 120 mg tablets was only 20% higher when co- administered with a high fat meal | * No | * Yes |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Vicodin®**  **(hydrocodone bitartrate/APAP), CII** | For the relief of moderate to moderately severe pain | * Hydrocodone: semi- synthetic narcotic analgesic and antitussive (opioid receptors) * APAP: Antipyretic activity is mediated through hypothalamic heat regulating centers; inhibits prostaglandin synthetase. | * Every 4 to 6 hours as needed for pain | * N/A | 5 mg/300 mg: total daily dosage should not exceed 8 tablets  7.5 mg/300 mg: total daily dosage should not exceed 6 tablets  10 mg/300 mg: total daily dosage should not exceed 6 tablets | * N/A | * No | * No |
| **Zohydro® ER (hydrocodone bitartrate), CII** | 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.  Limitations of Use   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve Zohydro ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate- release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. * Zohydro ER is not indicated as an as- needed (prn) analgesic. | Hydrocodone is a semi- synthetic opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. Hydrocodone acts as a full agonist, binding to and activating opioid receptors at sites in the peri-aquaductal and peri-ventricular gray matter, the ventro- medial medulla and the spinal cord to produce analgesia. The analgesia, as well as the euphorant, respiratory depressant and physiologic dependence properties of agonist opioids like hydrocodone, result principally from agonist action at the μ  receptors. | * Every 12 hours * Must be taken whole, one capsule at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Crushing, chewing, or dissolving capsules will result in uncontrolled delivery of hydrocodone and can lead to overdose or death | * Every 3- 7 days | * N/A | * Food has no significant effect on the extent of absorption of hydrocodone from Zohydro ER. * Although there was no evidence of dose dumping associated with this formulation under fasted and fed conditions, peak plasma concentration of hydrocodone increased by 27% when a Zohydro ER 20 mg capsule was administered with a high- fat meal. | * Yes; co- ingestion with alcohol may result in increased plasma levels and a potentially fatal overdose of hydro- codone | * No |
| **Exalgo®**  **(hydromorphone HCl), CII** | For the management of pain in opioid-tolerant patients severe enough to require daily, around-the- clock, long-term opioid treatment and for which alternative treatment | Hydromorphone, a semi- synthetic morphine derivative, is a hydrogenated ketone of morphine.  Hydromorphone is principally an agonist of | * Every 24 hours * Swallow tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a | * Every 3- 4 days | * There is no intrinsic limit to the analgesic effect of hydro- morphone. * Clinically, however, | * Can be administered without regard to food | * No | * No |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | options are inadequate.  Patients considered opioid tolerant are those who are taking for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral  hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid.  Limitations of Use   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve Exalgo for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. * Exalgo is not indicated as an as-needed (prn) analgesic. | mu-receptors, showing a weak affinity for kappa receptors. As an opioid agonist, the principle therapeutic action of hydromorphone is analgesia. The precise mechanism of action of opioid analgesics is not known but the effects are thought to be mediated through  opioid-specific receptors located predominantly in the central nervous system. | potentially fatal dose of hydromorphone |  | dosage limitations are imposed by the adverse effects, primarily respiratory depression, sedation, nausea, and vomiting, which can result from high doses. |  |  |  |
| **Dolophine®**  **(methadone HCl), CII** | Indicated for:   * Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.   Limitations of Use:   * + Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the | Methadone hydrochloride is a mu- agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid | * Every 8 to 12 hours * May exhibit cumulative effects with repeated dosing. | * Every 1- 2 days | * N/A | * N/A | * No | * No |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | greater risks of overdose and death with long-acting opioids, reserve Dolophine for use in patients for whom alternative treatment options (e.g., non- opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.   * Dolophine is not indicated as an as- needed (prn) analgesic. * Detoxification treatment of opioid addiction (heroin or other morphine-like drugs). * Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services. | addiction.  Some data also indicate that methadone acts as an antagonist at the N- methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone’s efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals. |  |  |  |  |  |  |
| **Avinza®**  **(morphine sulfate ER), CII** | 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.  Limitations of Use:   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve Avinza for use in patients for whom alternative treatment options (e.g., | Morphine sulfate, a pure opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine include dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release, physical dependence, and alterations of the endocrine and | * Every 24 hours * Avinza capsules must be taken whole. Crushing, chewing, or dissolving the pellets in Avinza will result in uncontrolled delivery of morphine and can lead to overdose or death * Contents of the capsules (pellets) may be sprinkled over applesauce and then swallowed if patient is able to reliably swallow the applesauce without chewing. * Do not administer Avinza pellets through | * Every 3- 4 days (in incre- ments not greater than 30 mg) | * The daily dose of Avinza must be limited to a maximum of 1600 mg/day. * Avinza doses of over 1600 mg/day contain a quantity of fumaric acid that has not been demon- strated to be safe, and which may result in serious renal toxicity. | * Can be administered without regard to food | * Yes; co- ingestion with alcohol can result in fatal plasma morphine levels | * No |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.   * Avinza is not indicated as an as-needed (prn) analgesic. and persist for an extended period of time. | autonomic nervous systems.  Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors located throughout the body.  Morphine acts as a full agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and  peri-ventricular grey matter, the ventro- medial medulla and the spinal cord to produce analgesia. | a nasogastric or gastric tubes.   * Avinza 90 mg and 120 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. |  |  |  |  |  |
| **Embeda®**  **(morphine sulfate/ naltrexone HCl ER), CII** | 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.  Limitations of Use   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve Embeda for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate- release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. * Embeda is not indicated as an as-needed (prn) analgesic. | * Every 12 or 24 hours * Swallow capsules intact. The pellets in the capsules are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of morphine and release of sufficient dose of naltrexone to precipitate withdrawal in opioid-dependent individuals * Contents of the capsules (pellets) may be sprinkled over applesauce and then swallowed if patient is able to reliably swallow the applesauce without chewing. * Do not administer Embeda pellets through a nasogastric or gastric tubes * Embeda 100 mg/4 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. | * Every 1- 2 days | * N/A | * Can be taken with or without food | * Yes; co- ingestion with alcohol may result in increased plasma levels and a potentially fatal overdose of morphine | * Yes |
| **Kadian®**  **(morphine** | For the management of pain severe enough to | * A frequency of either once daily (every 24 | * Every 1- 2 days | * N/A | * N/A | * No | * No |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **sulfate ER), CII** | require daily, around-the- clock, long-term opioid treatment and for which alternative treatment options are inadequate.  Limitations of Use:   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve Kadian for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. * Kadian is not indicated as an as-needed (prn) analgesic. |  | hours) or twice daily (every 12 hours)   * Kadian capsules must be taken whole. Crushing, chewing, or dissolving the pellets in KADIAN capsules will result in uncontrolled delivery of morphine and can lead to overdose or death * Contents of the capsules (pellets) may be sprinkled over applesauce and then swallowed if patient is able to reliably swallow the applesauce without chewing * Contents of the capsules (pellets) may be administered through a 16 French gastrostomy tube. * Do not administer Kadian pellets through a nasogastric tube |  |  |  |  |  |
| **MS Contin®**  **(morphine sulfate ER), CII** | For the management pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.  Limitations of Use   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve MS Contin for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to |  | * Every 8 or 12 hours * MS Contin tablets must be taken whole. Crushing, chewing, or dissolving tablets will result in uncontrolled delivery of morphine and can lead to overdose or death | * Every 1- 2 days | * N/A | * No significant differences in Cmax and AUC when taken while fasting or with a high- fat breakfast | * No | * No |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | provide sufficient management of pain.   * MS Contin is not indicated as an as-needed (prn) analgesic. |  |  |  |  |  |  |  |
| **Percocet®**  **(oxycodone HCl/ APAP), CII** | For the relief of moderate to moderately severe pain. | Oxycodone: semisynthetic pure opioid agonist whose principal therapeutic action is analgesia.  APAP: non-opiate, non- salicylate analgesic and antipyretic. The site and mechanism for the analgesic effect of APAP has not been determined. | * Every 6 hours as needed for pain | * N/A | * The total daily dose of APAP should not exceed 4 grams. | * N/A | * No | * No |
| **Opana® ER**  **(oxymorphone HCl), CII** | 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.  Limitations of Use   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve OPANA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate- release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. * OPANA ER is not indicated as an as- | Oxymorphone, an opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. The precise mechanism of analgesia, the principal therapeutic action of oxymorphone, is unknown. Specific central nervous system opioid receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In addition, opioid receptors have also been identified within the peripheral nervous system. The role that these receptors play in these drugs’ analgesic effects is unknown. | * Every 12 hours * Swallow tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxymorphone * Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth * Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating | * 3-7 days | * N/A | * Cmax was increased by   ~ 50% in fed subjects compared to fasted subjects.   * AUC   increased by  ~18% in a study in fed subjects following the admin- istration of oxymorphone hydrochloride extended- release tablets   * After single PO dose of 40 mg, a peak plasma level of 2.8 ng/ml is achieved at 1hour in fasted subjects and a peak of | * Yes; co- ingestion with alcohol can result in fatal plasma oxy- morphone levels | * No |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | needed (prn) analgesic. |  |  |  |  | 4.25 ng/ml is achieved at 2 hours in fed subjects with very little difference in the curves thereafter   * Administer on an empty stomach, at least one hour prior to or two hours after eating |  |  |
| **Nucynta® ER**  **(tapentadol ER), CII** | 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 * neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long- term opioid treatment and for which alternative treatment options are inadequate.   Limitations of Use:   * Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended- release opioid formulations, reserve Nucynta ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate- release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. * Nucynta ER is not | Centrally-acting synthetic analgesic. The exact mechanism of action is unknown.  Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI).  Analgesia in animal models is derived from both of these properties. | * Every 12 hours * Swallow tablets whole. The tablets are not to be cut, crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of tapentadol * Tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth | * Every 3 days (in incre- ments of no more than 50 mg twice daily) | * Maximum   total daily dose of Nucynta ER is 500 mg | * AUC and Cmax increased by 6% and 17%, respectively, when admin- istered after a high-fat, high-calorie breakfast * May be given with or without food | * Yes; co- ingestion with alcohol can result in fatal plasma tapentadol levels | * No |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | indicated as an as- needed (prn) analgesic. |  |  |  |  |  |  |  |

#### Table 5.2. Contraindications

|  |  |  |  |
| --- | --- | --- | --- |
| **Product** | **Contraindications** | | |
| **REFERENCE DRUG:**  **OxyContin® (oxycodone HCl ER), CII** | * Patients with significant respiratory depression Patients with known or suspected paralytic ileus and gastrointestinal obstruction * Patients with acute or severe bronchial asthma in an unmonitored setting or in Patients with hypersensitivity (e.g., anaphylaxis) to oxycodone the absence of resuscitative equipment | | |
| **Butrans®**  **(buprenorphine) Transdermal System, CIII** | * Patients with significant respiratory depression Patients with known or suspected paralytic ileus * Patients with acute or severe bronchial asthma in an unmonitored setting or in Patients with hypersensitivity (e.g., anaphylaxis) to buprenorphine the absence of resuscitative equipment | | |
| **Duragesic®**  **(fentanyl transdermal system), CII** | * Patients who are not opioid tolerant Patient with significant respiratory compromise, especially if adequate monitoring * Management of acute pain or intermittent pain, or in patients who require and resuscitative equipment are not readily available opioid analgesia for a short period of time Patients who have acute or severe bronchial asthma * Management of post-operative pain, including use after out-patient or day Patients who have or who are suspected of having paralytic ileus surgeries, (e.g., tonsillectomies) Hyper-sensitivity to fentanyl or any component of the transdermal system. * Management of mild pain Severe hypersensitivity reactions, including anaphylaxis have been observed * Management of intermittent pain with Duragesic | | |
| **Hysingla® ER**  **(hydrocodone bitartrate), CII** | * Patients with significant respiratory depression Patients with dnown or suspected paralytic ileus and GI obstruction * Patients with acute or severe bronchial asthma in an unmonitored setting or Patients with hypersensitivity to any components of Hysingla ER or the active in the absence of resuscitative equipment ingredient, hydrocodone bitartrate | | |
| **Vicodin®**  **(hydrocodone bitartrate/APAP), CII** | * Patients with hypersensitivity (e.g., anaphylaxis) to hydrocodone or Cross-sensitivity may occur in patients hypersensitive to other opioids acetaminophen | | |
| **Zohydro® ER**  **(hydrocodone bitartrate), CII** | * Patients with significant respiratory depression Patients with acute or severe bronchial asthma or hypercarbia * Patients with known or suspected paralytic ileus Patients with hypersensitivity to hydrocodone bitartrate or any other ingredients   in Zohydro ER | | |
| **Exalgo® (hydromorphone**  **HCl), CII** | * Opioid non-tolerant patients. Fatal respiratory depression could occur in Patients who have had surgical procedures and/or underlying disease resulting patients who are not opioid tolerant. in narrowing of the narrowing of the gastrointestinal tract, or have “blind loops” * Patients with significant respiratory depression of the gastrointestinal tract or gastrointestinal obstruction * Patients with acute or severe bronchial asthma in an unmonitored setting or in Patients with hypersensitivity (e.g., anaphylaxis) to hydromorphone or sulfite- the absence of resuscitative equipment containing medications * Patients with known or suspected paralytic ileus | | |
| **Dolophine®**  **(methadone HCl), CII** | * Patients with significant respiratory depression Patient with known or suspected paralytic ileus * Patients with acute or severe bronchial asthma in an unmonitored setting or in Patients with hypersensitivity (e.g., anaphylaxis) to methadone the absence of resuscitative equipment | | |
| **Avinza®**  **(morphine sulfate ER), CII** | * Patients with significant respiratory depression * Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment * Patients with known or suspected paralytic ileus * Patients with hypersensitivity (e.g., anaphylaxis) to morphine (or naltrexone, Embeda only) | | |
| **Kadian®**  **(morphine sulfate ER), CII** |
| **MS Contin®**  **(morphine sulfate ER), CII** |
| **Embeda®**  **(morphine sulfate/ naltrexone HCl ER), CII** |
| **Percocet®**  **(oxycodone HCl/APAP), CII** | * Patients with known hypersensitivity to oxycodone, acetaminophen, or any other component of this product * Patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment) |    | Patients with acute or severe bronchial asthma or hypercarbia Patients with suspected or known paralytic ileus |

|  |  |  |
| --- | --- | --- |
| **Product** | **Contraindications** | |
| **Opana® ER**  **(oxymorphone HCl), CII** | * Patients with significant respiratory depression * Patients with acute or severe bronchial asthma or hypercarbia * Patients with known or suspected paralytic ileus | * Patients with moderate or severe hepatic impairment * Patients with known hypersensitivity to oxymorphone, any other ingredients in Opana ER, or to morphine analogs such as codeine |
| **Nucynta® ER**  **(tapentadol), CII** | * Patients with significant respiratory depression * Patients with acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment * Patients with known or suspected paralytic ileus | * Patients with hypersensitivity (e.g. anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product * Patients who are receiving monoamine oxidase inhibitors (MAOI) or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events |

#### Table 5.3. Warnings and Precautions

|  |  |  |
| --- | --- | --- |
| **Product** | **Warnings and Precautions** | |
| **REERENCE DRUG:**  **OxyContin® (oxycodone HCl ER), CII** | * Addiction, Abuse, and Misuse * Life-Threatening Respiratory Depression * Neonatal Opioid Withdrawal Syndrome * Interactions with CNS Depressants * Use in Elderly, Cachectic, and Debilitated Patients * Use in Patients with Chronic Pulmonary Disease * Hypotensive Effects * Use in Patients with Head Injury or Increased Intracranial Pressure | * Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen * Use in Patients with Gastrointestinal Conditions * Use in Patients with Convulsive or Seizure Disorders * Avoidance of Withdrawal * Driving and Operating Machinery * Cytochrome P450 3A4 Inhibitors and Inducers * Laboratory Monitoring |
| **Butrans®**  **(buprenorphine) transdermal System, CIII** | * Addiction, Abuse, and Misuse * Life-Threatening Respiratory Depression * Neonatal Opioid Withdrawal Syndrome * Interactions with Alcohol, CNS Depressants, and Illicit Drugs * Use in Elderly, Cachectic, and Debilitated Patients * Use in Patients with Chronic Pulmonary Disease * QTc Prolongation * Hypotensive Effects * Use in Patients with Head Injury or Increased Intracranial Pressure | * Hepatotoxicity * Application Site Skin Reactions * Anaphylactic/Allergic Reactions * Application of External Heat * Patients with Fever * Use in Patients with Gastrointestinal Conditions * Use in Patients with Convulsive or Seizure Disorders * Driving and Operating Machinery * Use in Addiction Treatment |
| **Duragesic® (fentanyl**  **transdermal system), CII** | * Addiction, Abuse, and Misuse * Life-Threatening Respiratory Depression * Accidental Exposure * Neonatal Opioid Withdrawal Syndrome * Interactions with Central Nervous System Depressants * Use in Elderly, Cachectic, and Debilitated Patients * Chronic Pulmonary Disease * Head Injuries and Increased Intracranial Pressure * Hypotensive Effects | * Interactions with CYP3A4 Inhibitors and Inducers * Application of External Heat * Patients with Fever * Cardiac Disease * Hepatic Impairment * Renal Impairment * Use in Pancreatic/Biliary Tract Disease * Avoidance of Withdrawal * Driving and Operating Machinery |
| **Hysingla® ER**  **(hydrocodone bitartrate), CII** | * Addiction, Abuse, and Misuse * Life-Threatening Respiratory Depression * Neonatal Opioid Withdrawal Syndrome * Interactions with Central Nervous System Depressants * Use in Elderly, Cachectic, and Debilitated Patients * Use in Patients with Chronic Pulmonary Disease * Use in Patients with Head Injury and Increased Intracranial Pressure | * Hypotensive Effect * GI Obstruction, Dysphagia, and Choking * Decreased Bowel Motility * Cytochrome P450 CYP3A4 Inhibitors and Inducers * Driving and Operating Machinery * Interaction with Mixed Agonist/Antagonist Opioid Analgesics * QTc Interval Prolongation |
| **Vicodin® (hydrocodone bitartrate/APAP), CII** | * Hepatotoxicity * Serious Skin Reactions * Hypersensitivity/anaphylaxis * Respiratory Depression * Head Injury and Increased Intracranial Pressure * Acute Abdominal Conditions * Cough Reflex | * Special Risk Populations: Elderly/debilitated patients, severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture * Severe Hepatic or Renal Disease * Use with Other CNS Depressants, MAO Inhibitors, Tricyclic Antidepressants * Drug/Laboratory Test Interactions |
| **Zohydro® ER (hydrocodone bitartrate), CII** | * Addiction, Abuse, and Misuse * Life-Threatening Respiratory Depression * Neonatal Opioid Withdrawal Syndrome * Interactions with CNS Depressants * Elderly, Cachectic, Debilitated Patients * Use in Patients with Chronic Pulmonary Disease * Hypotensive Effect | * Patients with Head Injury or Increased Intracranial Pressure * Use in Patients with Gastrointestinal Conditions * Use in Patients with Convulsive or Seizure Disorders * Avoidance of Withdrawal * Driving and Operating Machinery * Cytochrome P450 CYP3A4 Inhibitors and Inducers |

|  |  |  |  |
| --- | --- | --- | --- |
| **Product** | **Warnings and Precautions** | | |
| **Exalgo®** | * Addiction, Abuse, and Misuse |  | Use in Patients with Head Injury and Increased Intracranial Pressure |
| **(hydromorphone HCl),** | * Life-threatening Respiratory Depression |  | Use in Patients with Gastrointestinal Conditions |
| **CII** | * Neonatal Opioid Withdrawal Syndrome |  | Sulfites |
| * Interactions with CNS Depressants |  | Use in Patients with Convulsive or Seizure Disorders |
| * Use in Elderly, Cachectic, and Debilitated Patients |  | Avoidance of Withdrawal |
| * Use in Patients with Chronic Pulmonary Disease |  | Driving and Operating Machinery |
| * Hypotensive Effects |
| **Dolophine®** | * Addiction, Abuse, and Misuse |  | Hypotensive effect |
| **(methadone HCl), CII** | * Life-Threatening Respiratory Depression |  | Use in Patients with Head Injury and Increased Intracranial Pressure |
| * Life-Threatening QT Prolongation |  | Use in Patients with Gastrointestinal Conditions |
| * Neonatal Opioid Withdrawal Syndrome |  | Use in Patients with Convulsive or Seizure Disorders |
| * Interactions with CNS Depressants |  | Avoidance of Withdrawal |
| * Use in Elderly, Cachectic, and Debilitated Patients |  | Driving and Operating Machinery |
| * Use in Patients with Chronic Pulmonary Disease |
| **Avinza®**  **(morphine sulfate ER), CII** | * Addiction, Abuse, and Misuse * Life Threatening Respiratory Depression * Neonatal Opioid Withdrawal Syndrome |      | Hypotensive Effect  Use in Patients with Head Injury and Increased Intracranial Pressure Use in Patients with Gastrointestinal Conditions |
| **Embeda®**  **(morphine sulfate/ naltrexone HCl ER), CII** | * Interaction with CNS Depressants |  | Use in Patients with Convulsive or Seizure Disorders |
|
| * Use in Elderly, Cachectic, and Debilitated Patients |  | Avoidance of Withdrawal |
| * Use in Patients with Chronic Pulmonary Disease |  | Driving and Operating Machinery |
| **Kadian®**  **(morphine sulfate ER), CII** |
| * Interactions with CNS Depressants and Illicit Drugs (Embeda) |
| **MS Contin®**  **(morphine sulfate ER), CII** |
| **Percocet®** | * Misuse, Abuse and Diversion of Opioids |  | Interactions with Other CNS Depressants |
| **(oxycodone** | * Respiratory Depression |  | Interactions with Mixed Agonist/Antagonist Opioid Analgesics |
| **HCl/APAP), CII** | * Head Injury and Increase Intracranial Pressure |  | Ambulatory Surgery and Postoperative Use |
| * Hypotensive Effect |  | Use in Pancreatic/Biliary Tract Disease |
| * Hepatotoxicity |  | Tolerance and Physical Dependence |
| * Serious Skin Reactions |  | Laboratory Tests |
| * Hypersensitivity / anaphylaxis |
| **Opana® ER** | * Addiction, Abuse, and Misuse |  | Use in Patients with Head Injury or Increased Intracranial Pressure |
| **(oxymorphone HCl),** | * Life Threatening Respiratory Depression |  | Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small |
| **CII** | * Neonatal Opioid Withdrawal Syndrome |  | Gastrointestinal Lumen |
| * Interactions with CNS Depressants |  | Use in Patients with Gastrointestinal Conditions |
| * Use in Elderly, Cachectic, and Debilitated Patients |  | Use in Patients with Convulsive or Seizure Disorders |
| * Use in Patients with Chronic Pulmonary Disease |  | Avoidance of Withdrawal |
| * Use in Patients with Hepatic Impairment |  | Driving and Operating Machinery |
| * Hypotensive Effect |
| **Nucynta® ER** | * Addiction, Abuse, and Misuse |  | Seizures |
| **(tapentadol), CII** | * Life-Threatening Respiratory Depression |  | Serotonin Syndrome Risk |
| * Neonatal Opioid Withdrawal Syndrome |  | Use in Patients with Gastrointestinal Conditions |
| * Interactions with CNS Depressants |  | Avoidance of Withdrawal |
| * Use in Elderly, Cachectic, and Debilitated Patients |  | Driving and Operating Heavy Machinery |
| * Use in Patients with Chronic Pulmonary Disease |  | Hepatic Impairment |
| * Hypotensive Effect |  | Renal Impairment |
| * Use in Patients with Head Injury or Increased Intracranial Pressure |

#### Table 5.4. Adverse Reactions

|  |  |
| --- | --- |
| **Product** | **Adverse Reactions** |
| **REFERENCE DRUG:**  **OxyContin® (oxycodone HCl ER), CII** | Most common adverse reactions (>5%) in adults were constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. Most frequently reported adverse events in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation. OxyContin may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock |
| **Butrans®**  **(buprenorphine) Transdermal System, CIII** | Most common adverse reactions (≥ 5%) include: nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash. The most common serious adverse drug reactions (all <0.1%) occurring during clinical trials with Butrans were: chest pain, abdominal pain, vomiting, dehydration, and hypertension/blood pressure increased. |
| **Duragesic®**  **(fentanyl transdermal system), CII** | The most common adverse reactions (≥5%) in a double-blind, randomized, placebo-controlled clinical trial in patients with severe pain were nausea, vomiting, somnolence, dizziness, insomnia, constipation, hyperhidrosis, fatigue, feeling cold, and anorexia. Other common adverse reactions (≥5%) reported in clinical trials in patients with chronic malignant or nonmalignant pain were headache and diarrhea. |
| **Hysingla® ER**  **(hydrocodone bitartrate), CII** | Most common treatment-emergent adverse events (≥ 5%) are constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence |
| **Vicodin® (hydrocodone bitartrate/APAP), CII** | The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis, Stevens-Johnson syndrome, toxic epidermal necrolysis. |
| **Zohydro® ER (hydrocodone**  **bitartrate), CII** | Most common adverse reactions (≥2%) include: constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, abdominal pain, edema peripheral, upper respiratory tract infection, muscle spasms, urinary tract infection, back pain and tremor. |
| **Exalgo®**  **(hydromorphone HCl), CII** | Most common adverse reactions (>10%) are: constipation, nausea, vomiting, somnolence, headache, and dizziness. The most common treatment-related serious adverse reactions from controlled and uncontrolled chronic pain studies were drug withdrawal syndrome, overdose, confusional state, and constipation. |
| **Dolophine®**  **(methadone HCl), CII** | Most common adverse reactions are: lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred. |
| **Avinza®**  **(morphine sulfate ER), CII** | Most common adverse reactions (≥10%) are constipation, nausea, somnolence, vomiting and headache. The most common serious adverse events reported with administration of Avinza were vomiting, nausea, death in patients with underlying malignancy, dehydration, dyspnea, and sepsis. |
| **Embeda® (morphine sulfate/**  **naltrexone HCl ER), CII** | Most common adverse reactions (>10%): constipation, nausea, and somnolence. |
| **Kadian® (morphine sulfate ER),**  **CII** |  |
| **MS Contin® (morphine sulfate ER),**  **CII** | In clinical trials, the most common adverse reactions with MS Contin were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoric mood, MS Contin may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock |
| **Percocet® (oxycodone HCl/APAP), CII** | The most frequently observed non-serious adverse reactions include lightheadedness, dizziness, drowsiness or sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus. Serious adverse reactions that may be associated with Percocet tablet use include respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and shock. Rare cases of agranulocytosis has likewise been associated with acetaminophen use. In high doses, the most serious adverse effect is a dose-dependent, potentially fatal hepatic necrosis. Renal tubular necrosis and hypoglycemic coma also may occur. . |
| **Opana® ER**  **(oxymorphone HCl), CII** | Adverse reactions in ≥2% of patients in placebo-controlled trials: nausea, constipation, dizziness (excluding vertigo), somnolence, vomiting, pruritus, headache, sweating increased, dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased, and abdominal pain. The most common serious adverse events reported with administration of oxymorphone hydrochloride extended-release tablets were chest pain, pneumonia and vomiting. |
| **Nucynta® ER**  **(tapentadol ER), CII** | The most common (≥10%) adverse reactions were nausea, constipation, dizziness, headache, and somnolence. |

**Table 5.5. Drug Interactions**

|  |  |  |
| --- | --- | --- |
| **Product** | **Drug Interactions** | |
| **REFERENCE DRUG:**  **OxyContin® (oxycodone HCl ER), CII** | * CNS Depressants * Drugs Affecting Cytochrome P450 Isoenzymes Diuretics * Mixed Agonist/ Antagonist and Partial Agonist Opioid Analgesics Anticholinergics * Muscle Relaxants | |
| **Butrans® (buprenorphine)**  **Transdermal System, CIII** | * Benzodiazepines Skeletal Muscle Relaxants * CNS Depressants Anticholinergics * Drugs Affecting Cytochrome P450 Isoenzymes | |
| **Duragesic® (fentanyl transdermal**  **system), CII** | * Central Nervous System Depressants MAO Inhibitors * Drugs Affecting Cytochrome P450 3A4 Isoenzymes Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics   + Anticholinergics | |
| **Hysingla® ER (hydrocodone**  **bitartrate), CII** | * Drugs Affecting Cytochrome P450 Isoenzymes * Central Nervous System Depressants * Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics | * MAO Inhibitors * Anticholinergics * Strong Laxatives |
| **Vicodin®**  **(hydrocodone bitartrate/APAP), CII** | * Central Nervous System Depressants Tricyclic Antidepressants * MAO Inhibitors | |
| **Zohydro® ER (hydrocodone bitartrate),**  **CII** | * Alcohol Interactions with Mixed Agonist/Antagonist Opioid Analgesics * CNS Depressants MAO Inhibitors * Drugs Affecting Cytochrome P450 Isoenzymes Anticholinergics | |
| **Exalgo® (hydromorphone HCl), CII** | * CNS Depressants Monoamine Oxidase Inhibitors (MAOI) * Mixed Agonist/Antagonist Opioid Analgesics Anticholinergics | |
| **Dolophine® (methadone HCl), CII** | * CNS Depressants Mixed Agonists/Antagonist and Partial Agonist Opioid Analgesics * Drugs Affecting Cytochrome P450 Isoenzymes Antidepressants * Potentially Arrhythmogenic Agents Anticholinergics   + Laboratory Test Interactions | |
| **Avinza®**  **(morphine sulfate ER), CII** | * Alcohol (Avinza, Embeda, Kadian only) Cimetidine * CNS Depressants Diuretics * Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics Anticholinergics * Muscle Relaxants P-Glycoprotein (PGP) Inhibitors * Monoamine Oxidase Inhibitors (MAOIs) | |
| **Embeda®**  **(morphine sulfate/ naltrexone HCl ER), CII** |
| **Kadian®**  **(morphine sulfate ER), CII** |
| **MS Contin®**  **(morphine sulfate ER), CII** |
| **Percocet® (oxycodone HCl/APAP), CII** | * Skeletal Muscle Relaxants Activated Charcoal * CNS Depressants Beta-Blockers * Agonist/Antagonist Analgesics Loop Diuretics * Alcohol Lamotrigine * Anticholinergics Probenecid * Oral Contraceptives Zidovudine | |
| **Opana® ER (oxymorphone HCl), CII** | * Alcohol Muscle Relaxants * CNS Depressants Cimetidine * Interactions with Mixed Agonist/ Antagonist and Partial Agonist Opioid Anticholinergics Analgesics | |

|  |  |  |
| --- | --- | --- |
| **Product** |  | **Drug Interactions** |
| **Nucynta® ER (tapentadol), CII** | * Alcohol * Monoamine Oxidase Inhibitors * CNS Depressants * Serotonergic Drugs | * Muscle Relaxants * Mixed Agonist/Antagonist Opioid Analgesics * Anticholinergics |

#### Table 5.6. Use in Specific Populations

|  |  |
| --- | --- |
| **Product** | **Use in Specific Populations** |
| **OxyContin®**  **(oxycodone HCl ER), CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. OxyContin is not recommended for use in women immediately prior to and during labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. * Nursing: Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving OxyContin. Do not initiate OxyContin therapy while nursing because of the possibility of sedation or respiratory depression in the infant. * Pediatric Use: Safety and efficacy of OxyContin have been established in pediatric patients ages 11 to 16 years. Safety of OxyContin in pediatric patients below the age of 11 years has not been established. * Geriatric Use: Reduce the starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients. Respiratory depression is the chief risk in elderly or debilitated patients, usually the result of large initial doses in patients who are not tolerant to opioids, or when opioids are given in conjunction with other agents that depress respiration. Titrate the dose of OxyContin cautiously in these patients. * Hepatic Impairment: A study of OxyContin in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration * Renal Impairment: 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. |
| **Butrans®**  **(buprenorphine) Transdermal System, CIII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Butrans is not for use in women immediately prior to and during labor, where use of short-acting analgesics or other analgesic techniques are more appropriate. * Nursing: Buprenorphine is excreted in breast milk. The amount of buprenorphine received by the infant varies depending on the maternal plasma concentration, the amount of milk ingested by the infant, and the extent of first pass metabolism. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of buprenorphine is stopped. * Pediatric Use: The safety and efficacy of Butrans in patients under 18 years of age has not been established. * Geriatric Use: Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in the elderly population to ensure safe use. * Hepatic Impairment: Butrans has not been evaluated in patients with severe hepatic impairment. As Butrans is intended for 7-day dosing, consider the use of alternate analgesic therapy in patients with severe hepatic impairment. |
| **Duragesic®**  **(fentanyl transdermal system), CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Fentanyl readily passes across the placenta to the fetus; therefore, Duragesic is not recommended for analgesia during labor and delivery. * Nursing: Fentanyl is excreted in human milk; therefore, Duragesic is not recommended for use in nursing women because of the possibility of effects in their infants. * Pediatric Use: The safety and effectiveness of Duragesic in children under 2 years of age have not been established. * Geriatric Use: Clinical studies of Duragesic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Monitor geriatric patients closely for signs of sedation and respiratory depression, particularly when initiating therapy with Duragesic and when given in conjunction with other drugs that depress respiration. * Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of Duragesic has not been fully evaluated. Avoid use of Duragesic in patients with severe hepatic impairment. * Renal Impairment: The effect of renal impairment on the pharmacokinetics of Duragesic has not been fully evaluated. Avoid use of Duragesic in patients with severe renal impairment. |
| **Hysingla® ER**  **(hydrocodone bitartrate), CII** | * Pregnancy Category: C   o There are no adequate and well-controlled studies of hydrocodone use during pregnancy. Based on limited human data in the literature, hydrocodone does not appear to increase the risk of congenital malformations. In animal reproduction and developmental toxicology studies, no embryotoxicity or teratogenicity was |

|  |  |
| --- | --- |
| **Product** | **Use in Specific Populations** |
|  | observed. Reduced fetal/pup body weights were observed at maternally toxic doses.   * Labor and Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Hydrocodone is not recommended for use in women immediately prior to and during labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. * Nursing: Hydrocodone has shown to be secreted in milk from both animal studies and clinical studies. The concentrations in milk were 5-fold less than in plasma in the peri-/postnatal study. Standard postpartum dosages of hydrocodone appear to be acceptable to use in women nursing newborns. Prolonged use of high dosages is not advisable. * Pediatric Use: safety and effectiveness has not been established in pediatric patients below the age of 18 years. * Geriatric Use: elderly subjects (greater than 65 years) compared to young adults had similar plasma concentrations of hydrocodone. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received Hysingla ER. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. * Hepatic Impairment: Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. No adjustment in starting dose with Hysingla ER is required in patients with mild or moderate hepatic impairment. Initiate therapy with ½ the initial dose of Hysingla ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression. * Renal Impairment: Patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function. Initiate therapy with ½ the initial dose of Hysingla ER in these patients and monitor closely for adverse events such as respiratory depression. |
| **Vicodin®**  **(hydrocodone bitartrate/APAP), CII** | * Pregnancy Category: C   o There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent.   * Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. * Nursing: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. * Pediatric Use: Safety and effectiveness in pediatric patients have not been established. * Geriatric Use: Clinical studies of hydrocodone bitartrate and acetaminophen tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. |
| **Zohydro® ER (hydrocodone**  **bitartrate), CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Opioids cross the placenta and may produce respiratory depression in neonates. Zohydro ER is not for use in women during and immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. * Nursing: Low concentrations of hydrocodone and hydromorphone in breast milk of nursing mothers using hydrocodone for postpartum pain control have been reported in published literature; Infants exposed to Zohydro ER through breast milk should be monitored for excess sedation, respiratory depression. * Pediatric Use: The safety and effectiveness in pediatric patients <18 years have not been established. * Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of the concomitant disease or other drug therapy. * Hepatic Impairment: No adjustment in starting dose with Zohydro ER is required in patients with mild or moderate hepatic impairment; however, in patients with severe hepatic impairment, start with the lowest dose, 10 mg. Monitor these patients closely for adverse events such as respiratory depression. * Renal Impairment: Patients with renal impairment have higher plasma concentrations than those with normal function. Use a low initial dose of Zohydro ER in patients with renal impairment and monitor closely for adverse events such as respiratory depression. |

|  |  |
| --- | --- |
| **Product** | **Use in Specific Populations** |
| **Exalgo®**  **(hydromorphone HCl), CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Exalgo is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. * Nursing: Low concentrations of hydromorphone have been detected in human milk in clinical trials. Withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped. Nursing should not be undertaken while a patient is receiving Exalgo since hydromorphone is excreted in the milk. * Pediatric Use: The safety and effectiveness of Exalgo in patients 17 years of age and younger have not been established. * Geriatric Use: Elderly patients have been shown to be more sensitive to the adverse effects of opioids compared to the younger population. Therefore, closely monitor elderly patients for respiratory and central nervous system depression when prescribing Exalgo, particularly during initiation and titration. * Hepatic Impairment: Start patients with moderate hepatic impairment on 25% of the Exalgo dose that would be used in patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with Exalgo and during dose titration. The pharmacokinetics of hydromorphone in severe hepatic impairment patients have not been studied. Use of alternative analgesics is recommended. * Renal Impairment: Start patients with moderate renal impairment on 50% and patients with severe renal impairment on 25% of the Exalgo dose that would be prescribed for patients with normal renal function. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with Exalgo and during dose titration. As Exalgo is only intended for once daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment. |
| **Dolophine®**  **(methadone HCl), CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Dolophine is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. * Nursing: Methadone is secreted into human milk. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone. Cases of sedation and respiratory depression in infants exposed to methadone through breast milk have been reported. Caution should be exercised when methadone is administered to a nursing woman. * Pediatric Use: The safety, effectiveness, and pharmacokinetics of methadone in pediatric patients below the age of 18 years have not been established. * Geriatric Use: Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. In general, start elderly patients at the low end of the dosing range, taking into account the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients. Closely monitor elderly patients for signs of respiratory and central nervous system depression. * Hepatic Impairment: Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways; therefore, patients with liver impairment may be at risk of increased systemic exposure to methadone after multiple dosing. Start these patients on lower doses and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression. * Renal Impairment: Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Since unmetabolized methadone and its metabolites are excreted in urine to a variable degree, start these patients on lower doses and with longer dosing intervals and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression. |
| **Avinza®**  **(morphine sulfate ER), CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Avinza is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. * Nursing: Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. * Pediatric Use: The safety and effectiveness of Avinza in pediatric patients below the age of 18 years have not been established. * Geriatric Use: The pharmacokinetics of Avinza have not been studied in elderly patients. In clinical studies of Avinza, 100 patients who received Avinza were age 65 and over, including 37 patients over the age of 74. No overall differences in safety were observed between these subjects and younger subjects. * Hepatic Impairment: Morphine pharmacokinetics are altered in individuals with cirrhosis. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted. * Renal Impairment: Morphine pharmacokinetics are altered in patients with renal failure. Adequate studies of the pharmacokinetics of morphine in patients with severe |

|  |  |
| --- | --- |
| **Product** | **Use in Specific Populations** |
|  | renal impairment have not been conducted. |
| **Embeda® (morphine sulfate/**  **naltrexone HCl ER), CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Embeda is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. * Nursing: Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. * Pediatric Use: The safety and effectiveness of Embeda in patients less than 18 years have not been established. * Geriatric Use: Clinical studies of Embeda did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Limited data are available on the pharmacokinetics of Embeda in geriatric patients. * Hepatic Impairment: The pharmacokinetics of morphine was found to be significantly altered in individuals with alcoholic cirrhosis. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted. * Renal Impairment: The pharmacokinetics of morphine are altered patients with in renal failure. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted. |
| **Kadian® (morphine sulfate ER),**  **CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Kadian is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. * Nursing: Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. * Pediatric Use: The safety and effectiveness of Kadian in patients less than 18 years have not been established. * Geriatric Use: Clinical studies of Kadian did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. * Hepatic Impairment: The pharmacokinetics of morphine was found to be significantly altered in individuals with alcoholic cirrhosis. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted. * Renal Impairment: The pharmacokinetics of morphine are altered patients with in renal failure. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted. |
| **MS Contin® (morphine sulfate ER),**  **CII** | * Pregnancy Category: C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. MS Contin is not recommended for use in women during and immediately prior to labor. * Nursing: Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. * Pediatric Use: The safety and effectiveness in pediatric patients below the age of 18 years have not been established. * Geriatric Use: The pharmacokinetics of MS Contin have not been studied in elderly patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. * Hepatic Impairment: Morphine pharmacokinetics are altered in individuals with cirrhosis. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted. * Renal Impairment: Morphine pharmacokinetics are altered in patients with renal failure. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted. |
| **Percocet®**  **(oxycodone HCl/ APAP), CII** | * Pregnancy Category: C   o Animal reproductive studies have not been conducted with Percocet. It is also not known whether Percocet can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Percocet should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards. Opioids can cross the placental barrier and have the potential to cause neonatal respiratory depression.   * Labor and Delivery: Percocet tablets are not recommended for use in women during and immediately prior to labor and delivery due to its potential effects on respiratory function in the newborn. * Nursing: Ordinarily, nursing should not be undertaken while a patient is receiving Percocet tablets because of the possibility of sedation and/or respiratory depression in the infant. Oxycodone is excreted in breast milk in low concentrations, and there have been rare reports of somnolence and lethargy in babies of nursing mothers taking |

|  |  |
| --- | --- |
| **Product** | **Use in Specific Populations** |
|  | an oxycodone/acetaminophen product. Acetaminophen is also excreted in breast milk in low concentrations.   * Pediatric Use: Safety and effectiveness in pediatric patients have not been established. * Geriatric Use: Special precaution should be given when determining the dosing amount and frequency of Percocet tablets for geriatric patients, since clearance of oxycodone may be slightly reduced in this patient population when compared to younger patients. * Hepatic Impairment: In a pharmacokinetic study of oxycodone in patients with end-stage liver disease, oxycodone plasma clearance decreased and the elimination half- life increased. Care should be exercised when oxycodone is used in patients with hepatic impairment. * Renal Impairment: In a study of patients with end stage renal impairment, mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance. Oxycodone should be used with caution in patients with renal impairment.. |
| **Opana® ER**  **(oxymorphone HCl), CII** | * Pregnancy: Category C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Opana ER is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. * Nursing: It is not known whether oxymorphone is excreted in human milk. Because many drugs, including some opioids, are excreted in human milk, caution should be exercised when Opana ER is administered to a nursing woman. * Pediatric Use: The safety and effectiveness of Opana ER in patients below the age of 18 years have not been established. * Geriatric Use: Initiate dosing with Opana ER in patients > 65 years of age using the 5 mg dose and monitor closely for signs of respiratory and central nervous system depression when initiating and titrating Opana ER. For patients on prior opioid therapy, start at 50% of the starting dose for a younger patient on prior opioids and titrate slowly. * Hepatic Impairment: Patients with mild hepatic impairment have an increase in oxymorphone bioavailability of 1.6-fold. In opioid-naïve patients with mild hepatic impairment, initiate Opana ER using the 5 mg dose and monitor closely for respiratory and central nervous system depression. Opana ER is contraindicated for patients with moderate and severe hepatic impairment. For patients on prior opioid therapy, start at the 50% of the dose for that a patient with normal hepatic function on prior opioids and titrate slowly. * Renal Impairment: Patients with moderate to severe renal impairment were shown to have an increase in oxymorphone bioavailability ranging from 57-65%. Start opioid- naïve patients with the 5 mg dose of Opana ER and titrate slowly while closely monitoring for respiratory and central nervous system depression. For patients on prior opioid therapy, start at 50% of the dose for a patient with normal renal function on prior opioids and titrate slowly |
| **Nucynta® ER**  **(tapentadol ER), CII** | * Pregnancy: Category C   o 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly   * Labor and Delivery: Nucynta ER is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. * Nursing: There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the breastfeeding child cannot be excluded. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of Nucynta ER is stopped. * Pediatric Use: The safety and efficacy of Nucynta ER in pediatric patients less than 18 years of age have not been established. * Geriatric Use: In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses. * Hepatic Impairment: Administration of tapentadol resulted in higher exposures and serum levels of tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The dose of Nucynta ER should be reduced in patients with moderate hepatic impairment (Child-Pugh Score 7 to 9). Use of Nucynta ER is not recommended in severe hepatic impairment (Child Pugh Score 10 to 15). * Renal Impairment: The safety and effectiveness of Nucynta ER has not been established in patients with severe renal impairment (CLCR <30 mL/min). Use of Nucynta ER in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known. |

#### Table 5.7. Pharmacokinetics

(lesser extent)

|  |  |  |  |
| --- | --- | --- | --- |
| **Product** | **Bioavailability** | **Major Metabolic Pathway(s)** | **Elimination Half-life** |
| **OxyContin®**  **(oxycodone HCl ER), CII** | 60-87% | * CYP3A * CYP2D6 | * 4.5 hours |
| **Butrans® (buprenorphine) Transdermal System, CIII** | * The absolute bioavailability of Butrans relative to IV administration, following a 7-day application, is approximately 15% for all doses (Butrans 5, 10, and 20 mcg/hour). | * CYP3A4 * UGT-isoenzymes (mainly UGT1A1 and 2B7) | * After removal of Butrans, the mean buprenorphine concentrations decrease approximately 50% in 12 hours (range 10-24 hours) with an apparent terminal half-life of approximately 26 hours. Due to this long apparent terminal half-life, patients may require monitoring and treatment for at least 24 hours. |
| **Duragesic®**  **(fentanyl transdermal system), CII** | * N/A | * CYP3A4 | ~20-27 hours |
| **Hysingla® ER**  **(hydrocodone bitartrate ER), CII** | * N/A; Compared to IR hydrocodone combination product, Hysingla ER at the same daily dose results in similar bioavailability but with lower maximum concentrations at steady state | * CYP3A4 * CYP2D6 | * ~7 to 9 hours |
| **Vicodin® (hydrocodone**  **bitartrate/APAP), CII** | * N/A | * O-demethylation * N-demethylation * 6-keto reduction | * 3.8 ± 0.3 hours (hydrocodone) |
| **Zohydro® ER (hydrocodone bitartrate), CII** | * N/A | * CYP3A4 * CYP2D6 | * ~8 hours |
| **Exalgo®**  **(hydromorphone HCl), CII** | * N/A | * Glucuronidation | * ~11 hours (range, 8-15 hours) |
| **Dolophine® (methadone HCl), CII** | 36-100% | * CYP3A4 * CYP2B6 * CYP2C19 * CYP2C9 Lesser * CYP2D6 extent | * 8-59 hours |
| **Avinza® (morphine sulfate ER),**  **CII** | <40% | * Glucuronidation * Sulfation | * ~24 hours |
| **Embeda® (morphine sulfate/**  **naltrexone HCl ER), CII** | 20-40% | * Glucuronidation * Sulfation | * ~29 hours |
| **Kadian® (morphine sulfate ER),**  **CII** | 20-40% | * Glucuronidation * Sulfation | ~11-13 hours |
| **MS Contin® (morphine sulfate ER),**  **CII** | ~20-40% | * Glucuronidation * Sulfation | * 2-4 hours; in some subjects it is 15 hours |
| **Percocet®**  **(oxycodone HCl/APAP), CII** | * 87% (oxycodone) | * CYP2D6 * Conjugation | * 3.51 ±1.43 hours (oxycodone) |

|  |  |  |  |
| --- | --- | --- | --- |
| **Product** | **Bioavailability** | **Major Metabolic Pathway(s)** | **Elimination Half-life** |
| **Opana® ER**  **(oxymorphone HCl), CII** | ~10% | * Reduction * Conjugation | 9.35±2.94-11.30±10.81 hours |
| **Nucynta® ER (tapentadol ER), CII** | ~32% | * Conjugation * CYP2C9 and CYP2C19 | * 5 hours |

APAP=acetaminophen; AUC=area under the curve; CNS=central nervous system; CR=controlled release; CYP=cytochrome; ER=extended release; GI=gastrointestinal; HCl=hydrochloride; IV=intravenous; MAO=monoamine oxidase; N/A=not available in Full Prescribing Information for product; PGP=P-glycoprotein

## Place of the Product in Therapy

* + 1. **onic Pain Disease Description**

#### Epidemiology

##### *Chronic Pain*

Chronic pain is a major public health problem. A consensus statement published by the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) asserted that “pain is one of the most common reasons people consult a physician, yet it frequently is inadequately treated, leading to enormous social costs in the form of lost productivity, needless suffering, and excessive health care expenditures” (AAPM and APS 1997).

Approximately 100 million adults in the US experience some type of chronic pain, and prevalence is increasing, due to (Institute of Medicine [IOM] 2011)

* aging of the population, and the concurrent increase in pain-associated diseases (eg, cancer, diabetes, arthritis) (IOM 2011, Cherry et al. 2010)
* increasing obesity, which is also associated with chronic illnesses in which pain is common (eg, diabetes) (IOM 2011)
* improved medical interventions that may save or extend the lives of people who experience catastrophic injury or cancer, and then live with the resulting chronic pain (IOM 2011)
* inadequately treated acute pain after surgery, leading to the development of chronic pain (IOM 2011; Rawal 2007)

The prevalence of pain in the US has risen based on National Health and Nutrition Examination Survey (NHANES) data collected from 1999 through 2004 (IOM 2011). An analysis of the World Health Organization’s (WHO) World Mental Health Survey (WMHS) estimated that 43% of American adults, amounting to approximately 100 million adults in 2010, have common chronic pain conditions (Tsang et al. 2008 and IOM 2011). Based on data compiled by the Centers for Disease Control and Prevention’s (CDC) National Center for Health Statistics (NCHS) from a 2010 civilian, non-institutionalized household survey, 16.6%, 28.4%, and 15.4% of American adults 18 years and older reported severe headache/migraine, low back pain, and neck pain, respectively, during the three months prior to the survey and 32.1% reported any joint pain in the 30 days prior to the survey (NCHS 2011). In the 2011 National Health Interview Survey (NHIS) of the U.S. civilian non- institutionalized adult population, 29% of participants reported chronic joint symptoms (Schiller et al. 2011).

Additionally, the prevalence of chronic pain in older non-institutionalized adults ranges from 18% to 57% dependent on which definition of chronic pain used (IOM 2011). According to the 2011 NHIS described above, arthritis and chronic joint symptoms were reported in 53% and 50% of adults greater than 75 years of age, respectively (Schiller et al. 2011). A rise in the prevalence of joint disorders with increasing age was noted in the survey data compiled by the NCHS described above (NCHS 2011) as was an increase in prevalence in any chronic pain condition with increasing age per the WMHS analysis (Tsang et al. 2008).

Demand for pain treatment is also increasing, due to greater awareness of—and improved treatments for— chronic pain, and improved access to healthcare (IOM 2011).

Risk factors for chronic pain include certain pathophysiologic conditions (eg, degenerative, neurologic, and metabolic conditions; rheumatologic changes; vascular issues), genetics, structural conditions (eg, skeletal malformations, degenerative spine disease, disk herniation), and injury/trauma (IOM 2011; Weisberg and Clavel 1999). Risk factors associated with low back pain in particular are obesity, lack of physical activity, lifting heavy objects, bending and twisting, age, medical conditions such as arthritis and osteoporosis, poor posture, psychological disorders such as stress and depression, and smoking (Chou et al. 2014).

41

##### *Opioid Abuse and Dependence*

Nonmedical use of prescription pain relievers is a serious public and individual health issue, even though its prevalence has been relatively constant over the last decade (between 1.9 – 2.1 million in a given 30-day period). After marijuana, pain relievers were the second most frequently abused drug in 2012, with an estimated number of people aged 12 years or older in the US who met DSM-IV criteria in the past year for either opioid analgesic abuse or opioid analgesic dependence increasing from 1.4 million in 2004 to 2.1 million in 2012 (Substance Abuse and Mental Health Services Administration [SAMHSA], National Survey on Drug Use and Health [NSDUH] 2012). Emergency department (ED) visits for nonmedical use of pharmaceuticals more than doubled (132%) from 2004 to 2011, accounting for approximately 1.25 million visits (SAMHSA, Drug Abuse Warning Network [DAWN] 2013). Involvement of opiates or opioids in these ED visits rose by 183% over the same time period. (SAMHSA, DAWN 2013).

##### *Acetaminophen*

The prevalence of acetaminophen usage at dosages >4 g/day is unknown (Blieden et al. 2014) However, database analyses suggest that approximately 20% of patients are prescribed opioid-acetaminophen combination products at an acetaminophen dosage ≥4 g/day (Duh et al. 2010; Mort et al. 2011). Patients prescribed combination opioid-acetaminophen treatment are at greater risk for hospitalization due to liver toxicity than those prescribed opioids only, especially at acetaminophen doses ≥4 g (Blieden et al. 2014). Approximately 63% of unintentional acetaminophen overdoses have been attributed to the use of opioid- acetaminophen combination products, and just over half of all ED visits due to unintentional acetaminophen overdose were related to opioid-acetaminophen combination products (Michna et al. 2010; Budnitz et al.

2011).

#### Pathophysiology

##### *Pain*

Pain is a complex and subjective phenomenon. Biologically, nociceptive pain is the result of the receipt and transmission of noxious stimuli by the nervous system (Schaible et al. 2004). Pain stimuli are translated by nociceptors into electric impulses that are transmitted to the spinal cord and brainstem (Schaible et al. 2004). The pain signal can be modified by interactions among numerous neurotransmitters and receptors (Schaible et al. 2004). These interactions may result in increased sensitivity to pain in and around an injured area, or descending pathways may reduce the perception of pain (Bourne et al. 2014). One such pathway involves endogenous opioids; when these activate the mu opioid receptor, pain transmission is blocked in the brain and descending pathways are activated, reducing the perception of pain (Bourne et al. 2014).

Neuropathic pain is caused by dysfunctional, diseased, or injured nerve tissue, in the peripheral or central nervous systems. Nerve damage or persistent stimulation may cause pain circuits to rewire themselves both anatomically and biochemically. This produces spontaneous afferent traffic from the peripheral or the central nervous system cells. This can be associated with increased pain based on autonomic nervous system activity, hyper-responsivity of peripheral or central neurons to painful stimulation, generation of afferent traffic that would normally only be caused by a painful stimulus by non-painful stimuli (eg, a light touch is interpreted as very painful), and spontaneous discharge of dorsal horn neurons that typically only subserve painful stimuli (Baumann and Strickland 2008).

##### *Opioid Abuse and Dependence*

Drugs that are liable to be abused, including opioids, substantially increase dopamine levels in the brain and alter the neurobiology of the individual. These changes ultimately lead to behaviors and symptoms typical of addiction, abuse, and dependence, such as drug seeking, reduced interest in normally pleasurable activities of daily life, poor impulse control, compulsive drug-related behaviors, and relapse (Volkow et al. 2004).

42

##### *Acetaminophen-Induced Hepatotoxicity*

Acetaminophen is metabolized by 3 pathways (McGill et al. 2013). The primary and secondary pathways produce metabolites that are then excreted; however, the tertiary pathway produces a toxic active metabolite (McGill et al. 2013). After a therapeutic dose of acetaminophen, this metabolite binds to liver glutathione (GSH) and is excreted (McGill et al. 2013). Upon acetaminophen overdose, however, GSH levels are reduced, and the unbound toxic metabolite binds to cellular proteins, ultimately inducing hepatocellular death and liver necrosis (McGill et al. 2013).

#### Clinical Presentation

Pain is a subjective, unpleasant, sensory and emotional experience (Loeser et al. 2011). Pain may be acute or chronic, lasting longer than several months (IOM 2011; Manchikanti et al. 2012). Chronic nonmalignant nonneuropathic pain refers to pain that is not caused by cancer or neuropathy; it includes muscle pain, inflammatory pain, and mechanical or compressive pain (eg, low back, neck, musculoskeletal) (Hooten et al.

2013; Chou et al. 2014; IOM 2011).

Accurate assessment of chronic pain is needed to tailor treatment appropriately, and should evaluate (Sarzi- Puttini 2012; Hooten et al. 2013; Chou et al. 2014)

* location, intensity, quality, onset, and duration of pain
* functional ability and goals, including issues with work and disability
* mechanism involved (eg, inflammation)
* psychosocial factors (eg, depression, substance abuse)
* other contributing factors or barriers to improvement

A medical history and physical are critical to this evaluation, as are quantitative scales used to characterize chronic pain and assess general health status, the severity of the pain, functioning, disability, and quality of life (Chou et al. 2014; Hooten et al. 2013). Imaging may be useful to identify physical pathologies contributing to the pain (Hooten et al. 2013).

Opioids and acetaminophen therapy are two important classes of pharmacotherapy used in pain management (See Section 2.2.2). Unfortunately, many opioid therapies are associated with a high risk for abuse, and may be ingested intact, perhaps in higher quantities than prescribed; crushed and swallowed, snorted, or smoked; or crushed, dissolved, and injected by patients and others, including people with addiction disorders (FDA 2013; Manchikanti et al. 2012; IOM 2011). Substance abuse is associated with problems at home, work, or school, or with family or friends; physical danger; and criminal and legal issues (SAMHSA, NSDUH 2012).

Substance dependence is considered more severe than abuse and involves health and emotional problems related to substance use, tolerance, withdrawal, not engaging in other activities in order to engage in substance use, spending a substantial amount of time engaging in substance use, unsuccessful attempts to reduce substance use, and using the substance more than or for longer than intended (SAMHSA, NSDUH 2012).

At dosages >4 g/day, acetaminophen can cause serious hepatotoxicity, and acetaminophen overdose is a serious concern, one which is high on the radar of organizations such as the American Liver Foundation (ALF), American Geriatric Society (AGS), Centers for Medicare and Medicaid Services (CMS), and FDA (Tylenol FPI 2009; ALF 2014; AGS 2009; CMS 2014; FDA Safe Use Initiative 2014). Hepatotoxicity associated with large overdoses of acetaminophen can result in nausea, vomiting, profound perspiration, malaise, and, if not treated promptly, liver failure and death (McNeil Consumer Healthcare 2009; Vicodin FPI 2014; Zydone FPI 2011; Percocet FPI 2011). Acetaminophen overdose frequently occurs as a result of accidental ingestion by children, or as a result of misdosing by adults (Budnitz 2011). The labeling for combination opioid-acetaminophen products contains hepatotoxicity warnings stating that acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death (Vicodin FPI 2014; Zydone FPI 2011; Percocet FPI

43

2013). Some epidemiologic evidence also indicates that acetaminophen is an ototoxic agent (Curhan et al. 2010; Curhan et al. 2012).

Because of the risks associated with acetaminophen overdose, in January 2011, FDA requested that manufacturers limit the amount of acetaminophen in each tablet or capsule of combination drug products to

≤325 mg by January 2014. In 2014, FDA instituted proceedings to withdraw from the market any combination products containing >325 mg of acetaminophen (FDA Safety Alert 2014).

#### Societal, Humanistic and/or Economic Burden

##### *Chronic Pain*

Family members and friends of those with chronic pain may find themselves taking on new and demanding roles, while at the same time coping with the physical and psychological changes in their loved one (IOM 2011). Over the long term, these negative changes can affect relationships and strain financial resources (IOM 2011). The physical, mental, and social well-being of those who suffer from chronic pain may deteriorate enough to cause depression (Dersh et al. 2002; Arnow et al. 2006; Von Korff et al. 2005).

Healthcare utilization, including ambulatory visits, ED visits, and hospital admissions, is significantly greater among patients with chronic pain than among those without chronic pain (Leider et al. 2011). The estimated annual economic cost of pain in the US, including the costs of health care and lost productivity, is $560 to $635 billion (2010 dollars) (IOM 2011). Care for chronic back pain alone costs $17.5 billion annually (as of 2000) (IOM 2011). A quarter of the cost of health care for pain is born by federal Medicare insurance; in 2008, 14% of Medicare expenditures went towards payments related to chronic pain ($65.3 billion) (IOM 2011). Other government agencies, such as the VA, also pay substantial amounts to address chronic pain, contributing to a total cost to the federal government of $99 billion (IOM 2011). Adding to this expense is lost tax revenue resulting from lost productivity (IOM 2011).

The results of a survey conducted from 2000 to 2007 found that, among patients with nonmalignant chronic pain, 99% were prescribed medication for their pain, and of these, 29% were prescribed ≥5 medications. In total, pain medication cost approximately $17.8 billion annually (2009 dollars) (Rasu et al. 2014).

Approximately 114 million prescriptions were written for opioids or opioid-like medications, with an annual cost of approximately $3.6 billion, or approximately 20% of the total annual cost of pain medication. Combination hydrocodone/acetaminophen was the most frequently prescribed opioid/opioid-like medication (39 million prescriptions from 2000 to 2007, for a total cost of $4.3 billion) (Rasu et al. 2014).

In 2000, outpatient visits for chronic pain made up approximately 11.3% of all office visits; in 2007, this had increased to approximately 14.3%. This trend is predicted to continue, reaching approximately 16% by 2015 (Rasu et al. 2014).

##### *Opioid Abuse and Dependence*

Substance abuse is frequently associated with comorbidities such as psychiatric disorders, pain, and abuse of other substances (McAdam-Marx et al. 2010; Baser et al. 2014).

In 2011, almost a quarter of all drug-related visits to the ED, or approximately 1.2 million visits, were the result of nonmedical use of pharmaceuticals. Approximately half of these ED visits were the result of pharmaceutical abuse or misuse. Pain relievers were the most common type of drug involved in these ED visits, with oxycodone, hydrocodone, and methadone associated with 12.1%, 6.6%, and 5.4%, respectively, of such visits in 2011 (SAMHSA, DAWN 2013).

Subsequent to an ED visit, many patients received further treatment in a hospital or other facility (SAMHSA, DAWN 2013). In 2007, the total costs of prescription opioid abuse were estimated at $55.7 billion, including

$25.6 billion for lost productivity, $25.0 billion for health care, and $5.1 billion for criminal justice costs

44

(Birnbaum 2011). Studies of the Veterans Health Administration, Medicaid, and commercial insurers have also demonstrated significantly higher healthcare utilization and costs for those who abuse opioids, versus those who do not (Baser et al. 2014; Rice et al. 2013; McAdam-Marx et al. 2010; White et al. 2005).

A 2014 analysis of claims data for approximately 9,000 abusers and 395,000 non-abusers (comparison cohort) found that the annual per-patient healthcare excess cost of opioid abuse was $10,627 (2012 dollars); this figure was largely driven by inpatient costs, followed by ED and rehabilitation costs. The per-member per- month (PMPM) cost of diagnosed opioid abuse was calculated to be $1.71 (Rice et al. 2014).

Abuse-deterrent technology has the potential to reduce these costs (see [Section 5.1](#_bookmark35)). Using data from the Truven Health Analytics database from 2009 through 2011, it has been estimated that use of reformulated extended-release (ER) oxycodone would result in a savings of $430 million (2011 dollars) in medical and drug costs among diagnosed and undiagnosed abusers ([Rossiter](#_bookmark37) et al. 2014). An extension of this analysis, which assumed that reformulated ER oxycodone would affect both direct and indirect costs to the same extent, estimated a total savings of approximately $1 billion (2011 dollars), with reductions in criminal justice costs, lost productivity, and medical and drug costs for caregivers making up the additional $605 million in savings ([Kirson](#_bookmark38) et al. 2014).

##### *Acetaminophen Overdose*

From 1993 to 2007, acetaminophen overdose was responsible for approximately 750,000 ED visits (average 50,103 per year, or 17.81 visits per 100,000 people per year) (Li et al. 2011). Approximately 33,000 patients were hospitalized annually for acetaminophen overdose from 2000 to 2006 (13.9 hospitalizations per 100,000 people over the 7-year period) (Manthripragada et al. 2011).

## Approaches to Treatment

#### Principle Treatment Approaches for Chronic Pain

Pharmacotherapy is the principle element of a comprehensive chronic pain treatment plan. Medications are often used in conjunction with other interventional, surgical, psychological, and rehabilitation treatment modalities. Treatment should be tailored to both the individual and the presenting problem.

There are three broad categories of drugs to treat chronic pain – nonopioid analgesics, opioid analgesics, and adjuvant analgesics. The nonopioid analgesics include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (Portenoy 2000). NSAIDs including aspirin, the non-selective and selective COX-inhibitors, and acetaminophen are commonly used for mild to moderate chronic nociceptive pain conditions. There is no evidence of their efficacy in treating neuropathic pain.

Opioids are used for pain ranging from moderate to severe depending on the specific opioid. Opioids are generally effective in treating nociceptive pain, but also have efficacy in neuropathic pain in some individuals (Dworkin et al. 2010).

Adjuvant agents or co-analgesics are drugs whose primary or initial indication was not for the treatment of pain, but may be used as analgesics in some chronic pain conditions. These include antidepressants, anticonvulsants, corticosteroids, muscle relaxants, local anesthetics, topical analgesics, and baclofen (Portenoy 2000 and APS 2008). Many of these agents such as tricyclic antidepressants, anticonvulsants, and topical agents (eg, capsaicin, lidocaine patches) are effective for treating neuropathic pain.

The WHO has promoted the three-step analgesic ladder as a framework for the rational use of analgesic medications in the treatment of cancer pain. Step I specifies the use of non-opioid analgesics. If this does not relieve the pain, step II recommends adding an opioid for mild to moderate pain. Step III comprises the use of an opioid for moderate to severe pain, with or without nonopioids. If needed, adjuvant drugs can be used at each step (WHO 1996). Although this analgesic ladder approach was developed for cancer pain, this approach

has been used for the treatment of other types of pain, as well. A more recent guideline for the treatment of cancer pain recommends moving away from the WHO analgesic ladder approach because cancer pain rarely progresses in a step wise fashion. The AGS recommends that all elderly patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy (AGS 2002; AGS 2009). Additionally, for elderly patients, sustained-release preparations are recommended as they increase compliance and dosing frequency may be reduced (Pergolizzi 2008).

#### Alternative Treatment Options for Chronic Pain

Chronic pain management can be carried out in many different ways. For many patients a combination of therapies (eg, rehabilitation, pharmacotherapy, interventional therapy, behavioral therapy, surgery) is the most successful approach.

Psychological therapies for chronic pain include individual cognitive behavioral therapy, hypnotic analgesia, and biofeedback treatment. Some interventional approaches to chronic pain management are diagnostic blocks, therapeutic blocks, implanted nerve stimulators, intraspinal drug delivery systems, and neuroablative procedures. Rehabilitation approaches include physical and occupational therapy, exercise, ergonomic modifications, thermal massage, transcutaneous electrical nerve stimulation, and orthotics. Surgery may also be indicated for the treatment of certain chronic pain conditions (eg, spinal disorders, arthritis) (Wisconsin Medical Society Task Force on Pain Management [WMS] 2004).

#### Place of OxyContin in Treatment of Chronic Pain

OxyContin Tablets are an extended-release oral formulation of oxycodone hydrochloride 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; 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 .

OxyContin is formulated with abuse-deterrent properties that are intended to make the tablets more difficult to manipulate for the purpose of misuse and abuse by intranasal, intravenous, or oral routes of administration.

Further, it has the potential to reduce risk of unintentional misuse and/or inadvertent medication error by patients or caregivers. Additionally, OxyContin has FDA-approved abuse-deterrent labeling claims, which indicate that the product is formulated with physicochemical barriers to abuse and is expected to result in a meaningful reduction in abuse.

Long-acting preparations may be preferred over short-acting agents in patients who require around-the-clock analgesic therapy because they allow less frequent dosing and may potentially decrease pain fluctuations and improve compliance (VA/DoD 2010). Given every 12 hours, OxyContin can simplify the therapeutic regimen.

Further, oxycodone formulations are considered step II and step III agents in the WHO analgesic ladder for pain (WHO 1996). Many guidelines for chronic pain conditions recommend the use of opioids for patients who have not responded to nonopioid analgesics (APS 2008 and Chou et al. 2009). The efficacy of OxyContin has been demonstrated in several studies in cancer-related pain, osteoarthritis-related pain, low back pain, pain associated with diabetic neuropathy, pain associated with post-herpetic neuralgia, and post-operative pain (see [Section 3.0](#_bookmark11)).

#### Chronic Pain Management Intervention Strategies Accompanying OxyContin

None.

#### Outcomes of Treatment for Chronic Pain

Patients on chronic opioid therapy should be regularly monitored for documentation of pain intensity and level of functioning, assessment of progress toward achieving therapeutic goals, presence of adverse events, and

adherence to prescribed therapy (Chou et al. 2009). Expected outcomes of treatment for chronic pain include pain reduction, improved physical function, patient satisfaction with and tolerability of therapies. There is a consistent pattern of pain reduction or continuing, stable pain control supporting the analgesic efficacy of OxyContin tablets across all studies, which involved patients with noncancer- or cancer-related pain syndromes.

Specific patient populations may show improvement in outcomes other than pain intensity. Along with improvements in pain, osteoarthritis patients treated with OxyContin versus placebo reported improvements in function and decreases in interference of pain with daily activities ([Roth](#_bookmark17) et al. 2000). In a placebo controlled trial among patients following surgery for total knee arthroplasty, use of scheduled OxyContin (and immediate-release oxycodone as needed) was associated with significant improvements in physical functioning and an average 2.3 day reduction in inpatient rehabilitation stay ([Cheville](#_bookmark27) et al. 2001).

Similar outcomes to those seen in clinical studies may be expected when used in appropriate patients.

#### Other Drug Development or Post-Marketing Obligations

##### *Postmarketing (Epidemiology) Studies*

To understand how the properties of reformulated OxyContin would impact real-world outcomes, Purdue designed a suite of postmarketing studies, in consultation with external experts in abuse, diversion, and epidemiology. The final study program also reflects the input of FDA and its Anesthetic & Life Support Drugs and Drug Safety & Risk Management Advisory Committees, to whom the study plans were submitted for review. The interim results of these studies have been reported to FDA on an ongoing basis as data are collected and analyzed.

Interpretation of these results should take into account the slight decrease in OxyContin dispensed by prescriptions from retail pharmacies over the study time periods. Following introduction of the reformulation, prescriptions for OxyContin decreased by 5% in the first year and 11% in the second year, compared to the one-year period prior to introduction of the reformulation.

The suite of epidemiologic studies includes some specifically designed to evaluate the effects of the reformulation on three types of real-world outcome measures of primary interest: (1) abuse and diversion, (2) adverse events in patients and therapeutic errors, and (3) accidental exposures resulting in calls to poison centers. Wherever possible, other opioid analgesics were used as comparators to differentiate between trends over time that were specific to OxyContin versus those that were general trends for opioid analgesics.

Data from these studies spanning the first two to two and one-half years of experience with the reformulated OxyContin indicate that its physicochemical properties are, in fact, having an impact on abuse, diversion, and unintentional medication error. Ongoing monitoring continues to assess if these trends change with time.

**Table 6**, presented on the next page, summarizes the endpoints of those epidemiologic studies where preliminary results are available. Following the table is a high-level overview of these studies’ designs and results that have been presented.

#### Table 6. Summary of Endpoints Measured by Select Epidemiologic Studies\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Studies** | **Abuse** | | | | **Patients** | | **Accidental Exposures** | |
| **Rates of Abuse** | **Diversion** | **Routes of Abuse** | **Poison Center Abuse Exposures** | **Poison Center Therapeutic Error Exposures** | **Analysis of Adverse Event Data** | **Poison Center Unintentional General Exposures** | **Analysis of Adverse Event Data** |
| **NAVIPPRO® –**  **Substance Abuse**  **Treatment Centers**a-d |  |  |  |  |  |  |  |  |
| **RADARS®**  **System – Poison Center Program**e |  |  |  |  |  |  |  |  |
| **RADARS®**  **System – Drug Diversion Program**f-h |  |  |  |  |  |  |  |  |
| **Abuser Cohort in Kentucky**i-k |  |  |  |  |  |  |  |  |
| **National Poison Data System – Poison**  **Centers**l-n |  |  |  |  |  |  |  |  |
| **Analysis of mortality data from adverse event reports**o |  |  |  |  |  |  |  |  |
| **Analysis of abuse, misuse, overdose, & medication error data from**  **adverse event reports**p |  |  |  |  |  |  |  |  |

\*Does not include all studies involving reformulated OxyContin and includes some supplemental studies not required by FDA

aButler et al. 2013; bChilcoat et al. CPDD, #103, 2012; cCassidy et al. CPDD, #88, 2012; dBlack et al. 2012;eChilcoat et al. AAPMR, #99, 2012; fSevertson et al. 2013; gChilcoat et al. AAPMR, #282, 2012; hBartelson et al. IASP, #PF085, 2012; iDeVeaugh-Geiss et al. CPDD,

#22, 2012; jLeukefeld et al. PainWeek, #358, 2012; kHavens et al. 2014; lCoplan et al. APS, 2012; mCoplan et al. CPDD, #121, 2012;

nCoplan et al. 2013; oSessler et al. PainWeek, #101, 2012; pSessler et al. PainWeek, #100, 2012

**Routes and Rates of OxyContin Abuse Among Patients Admitted to Substance Abuse Treatment Programs That Use NAVIPPRO®’s ASI-MV® Connect** (Butler et al. *J Pain*. 2013; Chilcoat et al. CPDD, #103, 2012; Cassidy et al. CPDD, #88, 2012; Black et al. 2012)

In this study, data were collected from a sample of individuals admitted for substance abuse treatment in a network of over 350 US centers that use the NAVIPPRO Addiction Severity Index-Multimedia Version (ASI- MV) Connect tool for assessment and treatment planning in adults. The ASI-MV collects self-reports of past 30-day substance abuse and identifies specific medications by presenting images, text, and audio, including actual product names, along with slang/street names. To facilitate correct identification, the images of both original and reformulated OxyContin included the tablet indicia (imprint marks) (Chilcoat et al. CPDD, #103, 2012; Cassidy et al. CPDD, #88, 2012; Black et al. 2012).

The study assessed both the prevalence of OxyContin abuse after introduction of the reformulated OxyContin, compared to historical abuse rates of the original formulation, and the changes in abuse of other opioid analgesics over the same timeframe. Abuse prevalence, with and without adjustment for the number of prescriptions in the relevant timeframe, was calculated. The study also evaluated whether reformulated OxyContin is less likely to be abused through routes of administration that require tampering (snorting, injecting, and smoking), compared to original formulation OxyContin and to other opioid analgesics

(Chilcoat et al. CPDD, #103, 2012; Cassidy et al. CPDD, #88, 2012; Black et al. 2012).

Prevalence rates and routes of administration were measured over the 14 months preceding availability of reformulated OxyContin (June 1, 2009 - August 8, 2010, the *before* period) and compared to the first 20 months following the introduction of reformulated OxyContin (August 9, 2010 - March 31, 2012, the *after* period) (Chilcoat et al. CPDD, #103, 2012; Cassidy et al. CPDD, #88, 2012).

In the before period, there were 69,002 assessments; in the after period, there were 71,494. Of the 140,496 total assessments, 26,453 (18.8%) reported abuse of at least one prescription opioid in the preceding 30 days. When analyzing only those assessments that reported OxyContin abuse, 4.06% of admissions in the before sample reported abuse of original OxyContin formulation, while in the after period only 2.41% reported abusing reformulated OxyContin (a 41% difference) (Chilcoat et al. CPDD, #103, 2012; Cassidy et al. CPDD, #88, 2012).

The prevalence of non-oral abuse (snorting, intravenous, smoking) of original OxyContin in the before period was 3.03%, compared to 1.02% for the reformulation in the after period (a 66% difference). Among the assessments reporting abuse of reformulated OxyContin, the prevalence of its abuse by snorting, injecting, and smoking was significantly lower for each route of administration in the after period than for original OxyContin in the before period (injection, 16% after vs. 36% before, respectively; p=.0002; snorting 25% vs. 53%, respectively, p<.0001; and smoking 4% vs. 6%, respectively, p=.0373) (Cassidy et al. CPDD, #88, 2012; Black et al. 2012).

The prevalence of abuse of the original formulation by the oral route in the before period was 2.15%, compared to 1.79% with the reformulation in the after period (a 17% difference). Even though there were fewer assessments reporting abuse of the reformulation by any route, 76% of them reported abuse by the oral route, compared to 55% reporting oral abuse of the original formulation in the before period (p<.0001), indicating a shift away from non-oral abuse after introduction of the reformulation (Cassidy et al. CPDD, #88, 2012).

The average frequency of abuse of OxyContin in the 30 days prior to admission was lower in the after period (7.48 days vs. 10.75) (Chilcoat et al. CPDD, #103, 2012).

Abuse of the original formulation of OxyContin persisted in the after period and is not reflected in the data above, as there was still some stock in the licit and illicit supply chains. Those reports became less frequent over time, likely due to decreasing availability of original OxyContin. The prevalence of reformulated OxyContin abuse reached a steady level soon after its introduction, at a 41% lower rate than that of original

OxyContin in the before period, and did not increase over the 20 months after its introduction, even as abuse of original OxyContin declined (Chilcoat et al. CPDD, #103, 2012).

The initial results of this study were published in the *Journal of Pain* and can be accessed at: <http://dx.doi.org/10.1016/j.jpain.2012.08.008>(Butler et al. 2013).

Further research is necessary to evaluate whether the lower proportion of individuals who abuse reformulated OxyContin is sustained beyond 20 months after its introduction.

**Measures of Abuse and Therapeutic Errors from the RADARS® System Poison Center Program**

(Chilcoat et al. AAPMR, #99, 2012)

In this study, data were collected from regional poison centers participating in the Poison Center Program of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System, an established surveillance system for prescription drug abuse. Participating poison centers cover over 80% of the US population. Calls and reports to poison centers about exposures to a drug product are a proxy measure of adverse events associated with misuse or abuse of a product. These data were used to estimate the change in the rate of exposures reported to poison centers for the reasons of 1) “intentional abuse” and 2) therapeutic errors that affect patients. Intentional abuse is defined by poison centers as an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect. Unintentional therapeutic error is an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Changes for OxyContin were assessed and compared to the comparator group of all other prescription opioids, by calendar quarter, before and after the introduction of reformulated OxyContin.

The before period was defined as October 2008 – September 2010 (before introduction of the reformulation) and October 2010 –June 2012 was defined as the period after introduction. Rates of abuse were calculated in two ways: one which adjusts for the size of the catchment population covered by the poison centers, which increased during the study period, and a second that adjusts for the availability of prescribed drug using a measure called unique recipients of dispensed drug (“URDD”), ie, the number of unique persons who redeemed a prescription for OxyContin or comparator opioids. The rates estimated for the period after introduction of the reformulation included poison center exposures for both original and reformulated OxyContin, due to continued, but decreasing, availability of the original formulation.

The average rate of abuse exposures for OxyContin decreased 39% (p<.001) using population-adjusted rates and decreased 31% (p<.001) using URDD-adjusted rates between the two time periods. The average rate of therapeutic errors (affecting patients) decreased 24% (p<.001) using population-adjusted rates and 14% (p<.001) using URDD-adjusted rates between the time periods.

For other prescription opioids, the average rate of abuse exposures increased nonsignificantly (0.9%) using population-adjusted rates, but decreased 10% (p=.001) using URDD-adjusted rates. The average rate of therapeutic errors increased nonsignificantly (1.9%) using population-adjusted rates, but decreased 9.2% (p=.002) using URDD-adjusted rates.

The data collected from the Poison Center Program of the RADARS System are based on voluntary calls to poison centers and reports from emergency departments. Therefore, they may underestimate changes in exposures due to reformulated OxyContin.

**The Drug Diversion Program of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System** (Severtson et al. *J Pain*. 2013; Chilcoat et al. AAPMR, #282, 2012; Bartelson et al. IASP,

#PF085, 2012)

This study compared the rates of drug diversion cases for OxyContin and comparator opioids reported by law enforcement officials participating in the RADARS® Drug Diversion Program for periods before (October 2008 – September 2010) and after (October 2010 –June 2012) the introduction of reformulated OxyContin. The Drug Diversion Program collects information on diversion of specific drug products in all 50 states. Law enforcement officials completed quarterly questionnaires eliciting information on the number of new cases of diversion and street price of specific diverted products in the US investigated by their respective agencies. In addition to population rates, adjustment for changes in drug availability (through legal channels) were accounted for by also calculating diversion rates per 1,000 unique recipients of dispensed drug (“URDD”) (Chilcoat et al.

AAPMR, #282, 2012; Bartelson et al. IASP, #PF085, 2012).

Also evaluated were the average street prices (dollars per milligram) of reformulated OxyContin compared to original formulation and to immediate-release (IR) oxycodone products. Prices were compared across drug formulations and time periods defined as: *before* introduction of reformulated OxyContin, 1Q2010; *during transition* to reformulated OxyContin, 3Q2010 - 4Q2010; and *after transition* to reformulated OxyContin, 1Q2011- 1Q2012 (Bartelson et al. IASP, #PF085, 2012).

The average diversion rate of OxyContin decreased by 56% (p<.001) using the population-adjusted rate and by 53% (p<.001) using the URDD rate following the introduction of reformulated OxyContin. These declines in rates of diversion were significantly greater than the changes observed for the comparator opioid group of all other prescription opioids. Reports of OxyContin diversion did not differentiate between original and reformulated OxyContin; therefore, declines in OxyContin diversion reports may understate the impact of the reformulation, due in part to continued availability of original OxyContin through legal and illegal channels for some time after introduction of the reformulation (Chilcoat et al. AAPMR, #282, 2012; Bartelson et al. IASP,

#PF085, 2012).

In the after transition period, the average street price of OxyContin was 19.8% lower than in the before period (p=.006) and was 28.1% lower than IR oxycodone (p<.001). The street price for IR oxycodone products increased 14.8% from the before period to the after transition period (p=.017) (Bartelson et al. IASP, #PF085, 2012).

The results of this study were published in the Journal of Pain and can be accessed at:<http://dx.doi.org/10.1016/j.jpain.2013.04.011> (Severtson et al. 2013).

Additional research is necessary to determine whether the decrease in diversion rates of OxyContin and lower street prices of reformulated OxyContin are maintained over time.

**Changes in Opioid Abuse Patterns in a Cohort Abusing OxyContin in Rural Kentucky** (Havens et al. *Drug Alcohol Depend*. 2014; DeVeaugh-Geiss et al. CPDD, #22, 2012; Leukefeld et al. PainWeek , #358, 2012)

In a sample of self-reported OxyContin abusers in a rural Kentucky county, changes in routes of administration and frequency of abuse of both OxyContin and immediate-release (IR) oxycodone were measured following the introduction of reformulated OxyContin. Structured interviews assessing opioid abuse, including route of administration and number of days of abuse in the past 30 days, were completed with 189 OxyContin abusers from December 2010 through September 2011. Participants reported retrospectively about their abuse of OxyContin in the period before the introduction of reformulated OxyContin (August 2010) and concurrently about their abuse of OxyContin following the introduction of the reformulated OxyContin (DeVeaugh-Geiss et al. CPDD, #22, 2012; Leukefeld et al. PainWeek , #22, 2012 ).

Following the introduction of the reformulation, the number of days of OxyContin abuse in the past 30 days decreased (DeVeaugh-Geiss et al. CPDD, #22, 2012; Leukefeld et al. PainWeek , #22, 2012 ).

In the before period, the frequency of abuse of the original formulation by snorting was 6.0 days. Following introduction of the reformulation the average number of snorting days decreased to 0.2 out of the past 30 days. The average injecting days was 8.6 in the before period and 0.01 days following the introduction of the reformulation. Abuse of OxyContin by swallowing increased slightly from 0.1 to 1.5 days in the past 30 days (Leukefeld et al. PainWeek , #22, 2012 ).

The prevalence of abuse by any route of administration was lower for reformulated OxyContin, compared to the route prevalences in the before period (33% vs. 74%). Changes in prevalence were greater for non-oral routes of administration: 39% vs. 5% for snorting and 41% vs. 0.5% for injecting; whereas swallowing was more prevalent for reformulated OxyContin (22%) than original OxyContin (2%) (DeVeaugh-Geiss et al. CPDD,

#22, 2012).

There was a small increase in the number of days per month of IR oxycodone injection and an increase in the prevalence of abuse by injection, after the reformulated OxyContin was introduced (DeVeaugh-Geiss et al.

CPDD, #22, 2012).

The results of this study were recently published online in *Drug and Alcohol Dependence* and can be accessed at: <http://dx.doi.org/10.1016/j.drugalcdep.2014.02.018>(Havens et al. 2014).

Further research is necessary to determine whether similar effects are observed in other populations that abuse OxyContin.

**Changes in Exposure Rates for OxyContin, other Single-entity Oxycodone Products, and Heroin in the National Poison Data System** (Coplan et al. *Pharmacoepidemiol Drug Saf*. 2013; Coplan et al. APS, 2012; Coplan et al. CPDD, #121, 2012)

This study assessed changes in OxyContin exposure cases received by the National Poison Data System (NPDS) before and after introduction of reformulated OxyContin. The NPDS is a national network of poison centers administered by the American Association of Poison Control Centers covering all poison centers in the US (Coplan et al. APS, 2012; Coplan et al. CPDD, #121, 2012). Unlike the RADARS® System Poison Center Program, NPDS also includes exposures to heroin.

Exposure cases are a proxy measure for adverse events. Calls to poison centers for information only are not classified as exposures. Calls or reports to poison centers are classified by reason/type of exposure by trained specialists. Exposures are classified into broad categories (eg, intentional and unintentional) and more specific reasons (eg, “intentional exposures” includes abuse, misuse, and suicide; “unintentional exposures” includes therapeutic errors, unintentional general, etc.). To provide comparison to any changes in OxyContin exposure cases, changes in exposure cases involving *other* single-entity oxycodone tablets (ie, products other than OxyContin that contain oxycodone as the only active ingredient), and changes in exposure cases to heroin were also assessed (Coplan et al. APS, 2012; Coplan et al. CPDD, #121, 2012).

The *before* period in this study was July 2009 through June 2010 (a one-year period before introduction of reformulated OxyContin) and the *after* period was October 2010 through December 2011. The break between the before and after periods (July – September 2010) allowed for transition between the original and reformulated product. The NPDS did not differentiate between the two formulations, so some cases after the transition period could have involved original formulation that was still available (Coplan et al. APS, 2012; Coplan et al. CPDD, #121, 2012).

The total number of OxyContin exposure calls (all reasons) decreased by 22% in the after period. Intentional exposure calls decreased by 19%, while intentional abuse calls decreased by 30%. Unintentional exposure calls decreased by 23%. Therapeutic error calls decreased by 17% and unintentional-general exposure calls (a proxy measure of accidental exposures, eg, among children) decreased by 38%. The number of exposure calls for other single-entity oxycodone products and heroin that were classified as intentional abuse, therapeutic errors, and unintentional-general increased in the after period (see **Table 7**) (Coplan et al. APS, 2012; Coplan et al. CPDD, #121, 2012).

To control for general trends prior to introduction of reformulated OxyContin that could affect interpretation of these data, an analysis of exposure-call trends for OxyContin, other single-entity oxycodone products, and heroin was also conducted for the timeframe predating the before period (July 2008 – June 2010). Over the 23 months preceding the before period, exposure calls for OxyContin increased by 8%, those for other single- entity oxycodone products increased by 11%, and those for heroin increased 5% (Coplan et al. APS, 2012; Coplan et al. CPDD, #121, 2012). Thus, any decrease in exposure calls following introduction of the reformulation were not due to an underlying trend.

To provide perspective, exposure call rates were also calculated as calls per 100,000 population (estimated) and calls per 100 prescriptions for the relevant drug. The population-based rate for all exposure calls decreased for OxyContin in the after period.

When adjusted per 100 prescriptions, however, the decreases were not as pronounced. In the after period, the number of prescriptions filled for other single-entity oxycodone products increased substantially. Thus, while the population-based rate increased, the rate per 100 prescriptions decreased, because of the marked increase in the denominator (see **Table 7**).

#### Table 7. Change in the Number of Exposure Calls Involving OxyContin, Other Single-entity Oxycodone Products (SEOs), and Heroin; Before and After Introduction of Reformulated OxyContin (Coplan et al. APS, 2012; Coplan et al. CPDD, #121, 2012)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Type of Exposure and Drug** | **Exposures per Quarter** | | **% Change (Before-After)** | **% Change adjusted by 100,000**  **population** | **% Change adjusted by 100 prescriptions** |
| **Before (July 2009-**  **June 2010)** | **After (Oct 2010-**  **Dec 2011)** |
| **All Exposures** | | | | | |
| OxyContin | 692.7 | 539.8 | -22 | -23 | -7 |
| Other SEOs | 1448.7 | 1684.8 | 16 | 14 | -14 |
| Heroin | 587.0 | 738.6 | 26 | 24 | N/A**‡** |
| **Intentional Exposures (all)** | | | | | |
| OxyContin | 390.5 | 316.2 | -19 | -20 | -3 |
| Other SEOs | 887.5 | 1057.2 | 19 | 16 | -12 |
| Heroin | 527.0 | 666.6 | 26 | 25 | N/A**‡** |
| **Intentional-Abuse Exposures** | | | | | |
| OxyContin | 130.2 | 90.6 | -30 | -31 | -17 |
| Other SEOs | 228.5 | 283.0 | 24 | 23 | -8 |
| Heroin | 355.7 | 460.6 | 30 | 28 | N/A**‡** |
| **Unintentional Exposures (all)** | | | | | |
| OxyContin | 242.5 | 185.8 | -23 | -24 | -9 |
| Other SEOs | 427.7 | 471.2 | 10 | 7 | -19 |
| Heroin | 28.0 | 33.6 | 20 | 18 | N/A**‡** |
| **Therapeutic Error Exposures\*** | | | | | |
| OxyContin | 161.2 | 133.8 | -17 | -18 | -2 |
| Other SEOs | 223.0 | 258.6 | 16 | 15 | -15 |
| **Unintentional-General Exposures** | | | | | |
| OxyContin | 75 | 46.2 | -38 | -39 | -26 |
| Other SEOs | 189.5 | 192.8 | 2 | 1 | -25 |
| Heroin | 22.2 | 27.0 | 21 | 20 | N/A**†** |

\*Not applicable to heroin as it is not used therapeutically.

**†**Heroin is not available by prescription in the US.

The results of this study were published online in the September 2013 issue of *Pharmacoepidemiology and Drug Safety* and can be accessed at: <http://onlinelibrary.wiley.com/doi/10.1002/pds.3522/full>(Coplan et al.. 2013).

The National Poison Data System data are based on voluntary calls to poison centers and, therefore, probably underestimate the true number of exposures. Further research is necessary to determine if these trends persist.

**Adverse Events Involving OxyContin Reported to Purdue Pharma L.P.** (Sessler et al. *Pharmacoepidemiol Drug Saf*. 2014; Sessler et al. PainWeek, #101, 2012; Sessler et al. PainWeek, #100, 2012)

Changes in the number of spontaneous adverse event (AE) reports involving OxyContin logged into Purdue’s Drug Safety and Pharmacovigilance department’s database (ARGUS) before and after the introduction of reformulated OxyContin (August 2010) were assessed in two separate studies (Sessler et al. PainWeek, #101, 2012; Sessler et al. PainWeek, #100, 2012).

In the first study, a search of ARGUS identified all US reports involving extended-release oxycodone with a fatal outcome that were reported from 3Q2009 through 2Q2012. Trends for all fatalities, those involving only overdose, and those involving both overdose and abuse were assessed separately (Sessler et al. PainWeek,

#101, 2012).

Of the 796 fatality case reports, the 366 that included the date of death (required to determine whether the death occurred before or after introduction of the reformulation) were analyzed in this study (see **Figure 6**) (Sessler et al. PainWeek, #101, 2012).

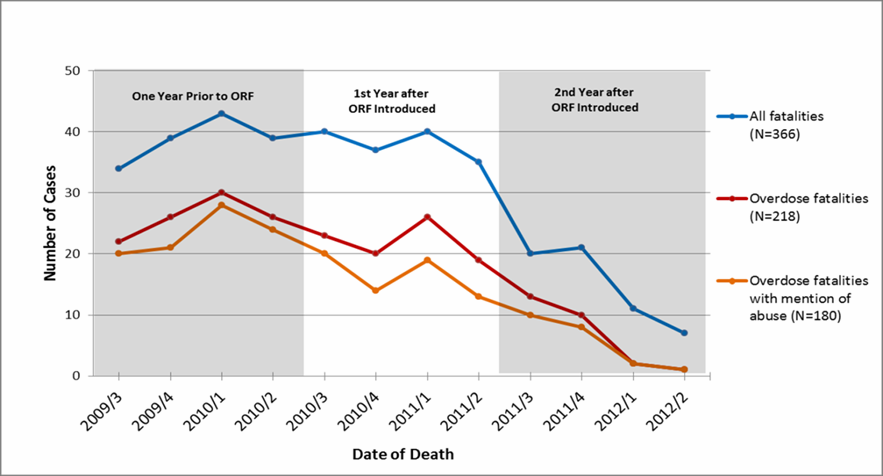
In the year before introduction of reformulated OxyContin, the number of fatal AE reports involving extended- release oxycodone averaged 39 per quarter (95% CI: 35 to 42). This average did not decline significantly in the first year after introduction of the reformulation (38 cases per quarter; 95% CI: 36 to 40). However, in the second year following introduction of the reformulation, the number of fatal AE reports declined by 62% to 15 cases per quarter (95% CI: 8 to 22) (Sessler et al. PainWeek, #101, 2012).

There were also changes in the subset of fatal AE reports in which overdose was specifically mentioned. In the year before introduction of the reformulated, the number averaged 26 per quarter (95% CI: 23 to 29). The quarterly average declined by 15% in the first year after introduction of reformulated OxyContin to 22 cases (95% CI: 19 to 25) and declined by 65% (9 cases; 95% CI: 3 to 15) in the second year after it was introduced

(Sessler et al. PainWeek, #101, 2012).

The quarterly average of fatal overdose cases where abuse was also specifically mentioned in the year before the reformulation was introduced was 23 (95% CI: 20 to 27). It declined by 29% in the first year after introduction of the reformulation (17 cases; 95% CI: 13 to 20) and by 78% to 5 cases (95% CI: 1 to 10) the second year after reformulation (Sessler et al. PainWeek, #101, 2012)..

#### Figure 6. Total Number of Fatalities Involving OxyContin Reported per Quarter between 3Q2009- 2Q2012\* (Sessler et al. PainWeek, #101, 2012)



\*Only AE reports with a date of death were analyzed. Reports received after 2Q2012 with a date of death before 2Q2012 are not yet included.

These results show a reduction in the number of fatal adverse event cases involving OxyContin reported to Purdue after reformulation of OxyContin. This decline in reports was greater the second year after the reformulation was introduced. All reports involving fatalities decreased, as did those specifically involving overdose, with or without a definite mention of abuse (Sessler et al. PainWeek, #101, 2012).

In the second study, a search of ARGUS was performed to identify all spontaneous AE US case reports involving extended-release oxycodone that were associated with drug abuse, intentional drug misuse, medication error/maladministration, or overdose that were received between January 1, 2010 and December 31, 2011. A specific OxyContin formulation (*original* or *reformulation*) was assigned to each case based on the receipt date or reporter information (Sessler et al. PainWeek, #100, 2012).

A total of 2,091 cases were identified – 1,272 of which were designated as original formulation and 819 of which were designated as reformulated OxyContin. The number of unique cases associated with drug abuse, medication error/maladministration, and overdose were all lower for reformulated OxyContin than for the original OxyContin formulation. The number of unique cases with an intentional drug misuse term was similar for reformulated OxyContin and original formulation. However, the numbers of cases in all four classes that were associated with a fatal outcome were markedly lower for reformulated OxyContin (see **Table 8**) (Sessler et al. PainWeek, #100, 2012).

#### Table 8. Change in Number of Spontaneous Adverse Event Reports\* in ARGUS Following Introduction of Reformulated OxyContin (Sessler et al. PainWeek, #100, 2012)

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse Event Report** | **Original OxyContin (Jan-Dec 2010)** | **Reformulated OxyContin (Jan-Dec 2011)** | **% Change** |
| **Drug Abuse** | | | |
| All | 894 | 499 | **-44** |
| Fatal | 48 | 14 | **-71** |
| **Intentional Drug Misuse** | | | |
| All | 146 | 150 | **3** |
| Fatal | 2 | 1 | **-50** |
| **Medication Error / Maladministration** | | | |
| All | 155 | 131 | **-16** |
| Fatal | 8 | 4 | **-50** |
| **Overdose** | | | |
| All | 240 | 120 | **-50** |
| Fatal | 162 | 79 | **-51** |

\*A report includes only one individual, but may contain more than one adverse event.

These results show that following the introduction of reformulated OxyContin, there were reductions in the number of spontaneous AE cases reported to Purdue where an extended-release oxycodone was associated with drug abuse, medication error, and overdose (Sessler et al. PainWeek, #100, 2012).

There are important limitations to these studies; therefore, their results should be cautiously interpreted. These studies are observational, rely on information that was spontaneously and voluntarily reported to Purdue, and reflect an unknown and potentially variable fraction of fatalities occurring in the US population. In addition, as a result of the coding convention used in the second study, some cases reported after introduction of the reformulation may have actually involved the original formulation of OxyContin. If that were, in fact, true, it would reduce the apparent effect of the reformulation. Lastly, as mentioned previously, there was a slight decrease in the number of OxyContin prescriptions dispensed by retail pharmacies over the study time periods (6-11%), which may account for a small part of the observed reductions in abuse and misuse-related adverse events and reported fatalities (Sessler et al. PainWeek, #101, 2012; Sessler et al. PainWeek, #100, 2012).

The results of this study were published online in the June 2014 issue of *Pharmacoepidemiology and Drug Safety* and can be accessed at: <http://onlinelibrary.wiley.com/doi/10.1002/pds.3658/full>(Sessler et al. 2014)

##### *Other Ongoing Studies*

In addition to those studies listed in [**Table 6**](#_bookmark8), other studies are underway, but have not yet been published in peer-reviewed journals. These include: surveys of changes in rates of abuse in schools and colleges; and changes in rates of opioid overdose and poisoning events in the Kaiser Permanente Health System following the introduction of reformulated OxyContin (Data on file). A poster on a study of changes in “doctor-shopping” for OxyContin following the introduction of the reformulation has been presented recently (Chilcoat et al. APS, 2014). Furthermore, the interim results of an additional study on internet monitoring for “recipes” of tampering with and “liking” of the reformulation has been published and is available at: <http://www.jmir.org/2014/5/e119/> (McNaughton et al. 2014).

Further, OxyContin is subject to post-marketing requirements authorized by FDA that include conducting epidemiological studies to evaluate whether the abuse-deterrent properties of OxyContin result in significant and meaningful decrease in misuse, abuse, addiction, overdose, and death in the community. Studies will be conducted in accordance with the FDA guidance on abuse-deterrent opioids to allow for FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of OxyContin (FDA 2015).

In addition, as a member of the ER/LA opioid analgesic class, studies assessing the serious risks of misuse, abuse, addiction, overdose, and death, as well as estimating the serious risk for the development of hyperalgesia and tolerance associated with the long-term use of ER opioids, including OxyContin, prescribed for the management of chronic pain will be conducted.

##### *OxyContin Risk Evaluation Mitigation Strategy*

Further, OxyContin is subject to the requirements of the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS). The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death. The REMS elements include a Medication Guide, Elements to Assure Safe Use, and a timetable for submission of assessments. Additional information can be found at [www.ER-LA-](http://www.er-la-opioidrems.com/)  [opioidREMS.com](http://www.er-la-opioidrems.com/).

#### Other Key Assumptions

None.

## Relevant Treatment Guidelines and Consensus Statement from National and/or International Bodies

There are many chronic pain treatment guidelines for different pain conditions that include recommendations for the use of opioids, including oxycodone. Some of the national treatment guidelines are listed with their recommendation in **Table 9.**

#### Table 9. Treatment Guidelines for Chronic Pain Conditions

|  |  |  |
| --- | --- | --- |
| **Organization/Society** | **Treatment Guidelines** | **Recommendation(s)** |
| **American Academy of Neurology** | Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy. *Neurology*. 2011;76:1758-1765 | * Opioids should be considered for the treatment of painful diabetic neuropathy. |
|  | Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*.  2004;63(6):959-965. | * There is class I evidence that long acting oral opioid preparations provide relief in treatment of postherpetic neuralgia. |
| **American College of Occupational and Environmental Medicine (ACOEM)** | American College of Occupational and Environmental Medicine. ACOEM guidelines for the chronic use of opioids. 2011. | * Opioid analgesics may be appropriate for select patients with chronic persistent pain that is not well-controlled with non-opioid treatment |
| **American College of Physicians and the American Pain Society** | Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007;147(7):478-491. | * Opioid analgesics are an option when used judiciously in patients with acute or chronic low back pain who have severe, disabling pain that is not controlled (or is unlikely to be controlled) with acetaminophen and NSAIDs. |
| **American College of Rheumatology** | Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012 Apr;64(4):465-74. | * Opioids are conditionally recommended in patients who had an inadequate response to initial therapy. * Opioids are strongly recommended in patients with symptomatic osteoarthritis who were unwilling to undergo or are not candidates for total joint arthroplasty after failing medical therapy. |
| **American Geriatric Society** | American Geriatric Society. Pharmacological management of persistant pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331- 1346. | * All patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy. |
| **American Pain Society** | Chou R, Fanciullo GJ, Fine PG, et al. Opioid treatment guidelines: clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130*.* [**American Pain Society-and American Academy of Pain Medicine**] | * Chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic noncancer pain. |
|  | American Pain Society*. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. 6th ed. Glenview, IL:  American Pain Society; 2008. | * Opioid analgesics should be added to nonopioids to manage pain that does not respond to nonopioids alone. * Long duration of action of controlled- release and transdermal opioids lessens severity of end-of-dose pain and often allows patients to sleep through the night. |

|  |  |  |
| --- | --- | --- |
| **Organization/Society** | **Treatment Guidelines** | **Recommendation(s)** |
| **American Society of Anesthesiologists** | American Society of Anesthesiologists. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology*.  2010;112(4):810-833. | * As part of a multimodal pain management strategy, extended-release oral opioids should be used for neuropathic or back pain patients. |
| **American Society of Interventional Pain Physicians (ASIPP)** | Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic noncancer pain: part I – evidence assessment. *Pain Physician*. 2012;15:S1- S66. | * Opioid therapy may improve quality of life parameters. |
|  | Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP): Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part 2 - Guidance. *Pain Physician*. 2012;15:S67-S116. | * Chronic opioid therapy may be continued, with continuous adherence monitoring, modified at any time during this phase, with fair evidence showing effectiveness of opioids in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects. * Specific to initiating and maintaining chronic opioid therapy for ≥90 days, clinicians must understand the effectiveness and adverse consequences of long-term opioid therapy in chronic non- cancer pain and its limitations. * For severe pain, first line therapy may include hydrocodone, oxycodone, hydromorphone, or morphine. * In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. |
| **International Association for the Study of Pain (IASP)** | Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85(3 Suppl):S3-14. | * Opioid analgesics have shown efficacy in several high-quality RCTs involving patients with different types of NP. * Opioid analgesics are recommended as second-line treatments that can be considered for first-line use in certain clinical circumstances. * Because the optimal opioid dosage varies substantially from patient to patient, patients must undergo individualized opioid titration, using dosages that have shown efficacy in NP trials and typically using extended-release formulations for long-term treatment. |

|  |  |  |
| --- | --- | --- |
| **Organization/Society** | **Treatment Guidelines** | **Recommendation(s)** |
|  | Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis.* 2007;44(Suppl 1):S1-26. | * For pain that is moderate to severe in intensity treatment with a strong opioid analgesic is recommended on the basis of the consistent efficacy of this class of medications in patients with inflammatory and neuropathic pain. * Once an effective dosage of a short-acting medication is determined, treatment can be switched to a long-acting medication, which is more convenient for patients and may also provide a more consistent level of pain relief. |
| **National Opioid Use Guideline Group** | National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain.  Version 5.6. April 2010. Available at: [http://nationalpaincentre.mcmaster.ca/opioid/.](http://nationalpaincentre.mcmaster.ca/opioid/) | * Opioids are more effective than placebo for chronic, noncancer pain and function. * CR formulations are recommended for the elderly for reasons of compliance |
| **Veterans Health Administration, Department of Defense** | Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain. May 2010. | * Long-acting preparations may be preferred over short-acting agents in patients who require around-the-clock analgesic therapy because they allow less frequent dosing and, potentially, may decrease pain fluctuations and improve compliance. * This guideline supports the use of long- acting opioids in a scheduled manner for chronic pain, rather than the use of supplemental or as-needed (PRN) opioids for exacerbations. |

## 2.3. Evidence for Pharmacogenomic Tests and Drugs

There is no information on the evidence for pharmacogenomic tests and drugs available.

**3. SUPPORTING CLINICAL EVIDENCE**

### Summarizing Key Clinical Studies

All OxyContin clinical studies in adult patients utilized the original OxyContin Tablets formulation.

## Published and Unpublished Data and Clinical Studies Supporting Labeled Indications

#### Studies in Patients with Cancer-related Pain

Wang W, OuYang X, Yu Z, Chen Z. Clinical application of OxyContin hydrochloride controlled release tablets in treatment of pain suffered from advanced cancer. *Chin Ger J Clin Oncol*. 2012;11:419-421.

Study Dates: Aug 2005-Nov 2006

This study evaluated the efficacy and safety of OxyContin in the treatment of moderate to severe pain in patients with terminal cancer and assessed improvement in patients’ quality of life (QOL).

Male and female patients with moderate to severe pain associated with terminal cancer (phase IV according to TNM classification) were included in the study. Patients who were not previously treated with analgesics or used weak analgesics were initiated on OxyContin 10 mg twice daily. Patients who were using morphine previously were started on a dose of OxyContin that was equivalent to one-half of the morphine regimen. Dose titration was permitted until ideal analgesic effects were obtained, and each patient was treated for ≥15 days.

Pain was assessed using pain remission degree (0 degree=pain was not relieved; 1 degree=mild remission (~1/4); 2 degree=moderate remission (~1/2); 3 degree=obvious relief (~3/4); 4=complete remission (pain disappeared) and pain relief rate (percentage of patients whose pain was relieved by ≥2 degrees). QOL score was based on five parameters: appetite, sleep, daily life, mental status, and interpersonal intercourse before and after medication. Adverse events (AEs) were also recorded.

Sixty-eight patients (median age, 51.4 years; age range, 29-72 years) were included in the study (n=18, moderate pain vs. n=50, severe pain). The initial daily dose of OxyContin ranged from 10 mg to 120 mg (n=45,

≤30 mg/day; n=12, 31-60 mg/day; n=11, 61-120 mg/day). The final titrated dose of OxyContin was ≤30 mg/day for 30 patients, 31-60 mg/day for 16 patients, 61-120 mg/day for 18 patients, and ≥120 mg/day for 4 patients.

By day 15 of OxyContin treatment, 18 patients with moderate cancer pain had at least moderate pain remission, of which 12 had complete pain remission (degree 4) as shown in **Table 10**. Of the 50 patients with severe cancer pain, 47 patients achieved at least moderate pain remission, and 15 patients had complete remission while another 28 patients reported obvious pain relief.

#### Table 10. Cancer Pain Remission Degree by Day 15 of OxyContin Treatment

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Pain Degree** | **Cases** | **Pain Remission Degree** | | | | | **Pain Relief Rate (%)** |
| **0** | **1** | **2** | **3** | **4** |
| Moderate | 18 | 0 | 0 | 1 | 5 | 12 | 100.0% |
| Severe | 50 | 1 | 2 | 4 | 28 | 15 | 94.0% |
| Total | 68 | 1 | 2 | 5 | 33 | 27 | 95.6% |

QOL scores at day 15 of OxyContin treatment were compared to scores prior to treatment. Patients’ appetite, sleep, daily life, mental status, and interpersonal intercourse significantly improved after therapy compared to baseline (p<0.01).

The following AEs were observed: constipation, nausea, vomiting, dizziness, and dysuria. With the exception of constipation, AEs were of low occurrence. Psychological dependence, serious AEs, and drug abuse were reportedly not observed.

Mercadante S, Ferrera P, David F, Casuccio A. The use of high doses of oxycodone in an acute palliative care unit. *Am J Hosp Palliat Care*. 2011;28:242-244.

Study Dates: 2006-2008

A 3-year, retrospective chart review assessed the safety and efficacy of high-dose controlled-release oxycodone (CRO) for the management of cancer pain in adult patients admitted to an acute palliative care unit.

Data was collected for patients who were prescribed CRO at discharge and were divided into three groups based on their daily CRO dose: low-dose (<120 mg), moderate-dose (120-240 mg), and high-dose (>240 mg). Pain intensity was assessed using an 11-point (0-10) numerical rating scale (NRS). Adverse events were evaluated using a scale from 4-point scale (0=not at all, 1=slight, 2=a lot, 3=awful). Patients were discharged when doses stabilized and pain control had been achieved (defined as pain intensity of 4 on a NRS and 2-3 doses of opioids as needed for breakthrough pain and tolerable adverse effects).

A total of 212 patients (mean age, 62.4±13.2 years; 118 males, 94 females) were prescribed CRO at discharge (n=129, low-dose; n=43, moderate-dose; n=40, high-dose). The overall mean CRO dose was 141±167 mg (range, 10-960 mg). The mean CRO doses of per treatment group are presented in **Table 11**. Doses were significantly lower in older patients (p<0.0005). The mean admission time was 4.8 (+3.2) days. At hospital discharge, mean pain intensity was 2.9±1.9. Adverse events at hospital discharge were deemed mild and unrelated to CRO doses by investigators; however, specific adverse events were not reported in the study.

#### Table 11. Mean Doses of OxyContin in Patients Discharged From an Acute Palliative Care Unit

|  |  |  |
| --- | --- | --- |
| **OxyContin Treatment Groups** | **Number of Patients (N=212)** | **Mean Dose of OxyContin (mg)** |
| Low-dose (<120 mg/day) | 129 | 48.4±25 |
| Moderate-dose (120-240 mg/day) | 43 | 156.5±30.5 |
| High-dose (>240 mg/day) | 40 | 435±196 |

Ravera E, Di Santo S, Bosco R, Arboscello C, Chiarlone R. Controlled-release oxycodone tablets after transdermal-based opioid therapy in patients with cancer and non-cancer pain. *Aging Clin Exp Res*. 2011;23(5- 6):328-332.

An open-label, multicenter, observational study evaluated the efficacy of controlled-release oxycodone (CRO) therapy in patients with cancer and noncancer pain who obtained no or partial pain relief after transdermal opioid therapy (TTD).

Patients with persistent cancer or noncancer pain and were using TTD therapy for at least 5 days were eligible to participate. Enrolled patients were switched to CRO every 12 hours, and assessments occurred at baseline (T0), 3 days (T3), 7 days (T7) and 21 days (T21) later. The primary efficacy endpoint was pain intensity rated on an 11-point numerical rating scale (NRS; 0=no pain, 10=maximum severity). The secondary objective was to assess patients’ QOL based on pain interference on the following attributes using an 11-point NRS (0=no pain interference; 10=maximum interference): sleep quality, appetite, walking capacity, self-care, daily activities mood and concentration.

Forty-one patients (males, n=20; females, n=21; mean age, 65.21±12.71) were included in the study, of whom 27 experienced persistent cancer and 14 had noncancer pain. Prior TTD therapy included fentanyl TTD (n=25; mean daily dose=52.17±28.11 mcg) and buprenorphine (n=16; mean daily dose=65.96±35.36 mcg). The mean initial daily dose of CRO was 68.75 mg, which increased and stabilized to 72.39 mg after 7 days. Mean NRS pain score was 6.71±1.84, and after three days of CRO therapy, pain significantly decreased by 38.83% (p<0.001) and significant reduction was maintained throughout the 21-day period (T0-T7:-59.71%, p<0.001;

T0-T21: -65.75%, p<0.001). At baseline, 56.10% of patients reported severe pain with NRS scores of 7-10, and by day 21, this percentage decreased to 2.56%. QOL significantly improved with CRO treatment (p<0.001) and within 21 days, mean pain impact scores for sleep quality, appetite, walking capacity, self-care, daily activities, mood and concentration decreased by 1.74 to 3.74 points. No deaths occurred, and no patients discontinued therapy. No additional safety results provided.

Li X-M, Liu D-Q,Wu H-Y,Yang C, Yang L. Controlled-release oxycodone alone or combined with gabapentin for management of malignant neuropathic pain. *Chin J Cancer Res*. 2010;22(1):80-86.

Location: 1 center in China; Study Dates: Jun 2005-Nov 2008

An open-label, observational study was conducted to evaluate the efficacy and safety of controlled-release oxycodone (CRO) monotherapy or in combination with gabapentin (OG) for the management of moderate to severe pain associated with malignant neuropathy.

Adult patients (age, 18-80 years) with moderate or severe neuropathic cancer pain caused by an active cancer infiltrating or compressing nervous structures or due to chemotherapy, pain intensity score of ≥4 on a numerical rating scale (NRS; 0-10) in the 24 hours preceding the screening visit, life expectancy ≥30 days, and Karnofsky performance status (KPS) ≥40 were eligible to participate in the study. Exclusion criteria included: inability to take oral medications; serum creatinine >1.5 mg/mL or creatinine clearance <60 mL/min; current opioid or non-opioid analgesic, gabapentin, and other adjuvant medications; chemotherapy from seven days prior to screening through the study; radiotherapy to the lesion causing pain from 15 days prior to screening through the study. Hormone therapy was permitted if started before the study; dose changes were not allowed. If new pain developed or if the patient experienced intolerable side effects, they were withdrawn from the study.

The study consisted of two consecutive phases: (I) patients received one week of CRO monotherapy, with a starting dose of 10 mg every 12 hour that could be titrated based on patients’ pain intensity, (II) patients were placed in either the CRO group (NRS<4, day 8) or the OG group (NRS≥4, day 8); therapy continued for an additional two weeks. In the CRO group, doses could be titrated according to patients’ pain scores. In the OG group, CRO doses remained constant while gabapentin doses could be titrated from the initial dose of either 300 mg three times daily (patients <60 years of age) or 100 mg three times daily (patients > 60 years of age), to a maximum daily dose of 3200 mg. Immediate-release morphine tablets every 2-4 hour as needed was permitted for breakthrough pain. Prophylactic bowel regimens and anti-emetics were started simultaneously with initiation of CRO therapy. Mean pain intensity was assessed by NRS at baseline (day 0), days 8, 15, and

22. Adverse events were also recorded.

Sixty-three patients were enrolled in the study, of which 58 patients (CRO, n=22; OG, n=36) were assessed in the efficacy analysis. During Phase I (at day 8), the overall mean daily dose (MDD) of CRO was 62.64 mg (SD=32.35). By day 15, the MDD of CR oxycodone in the CRO monotherapy group significantly increased compared to day 8 (71.43 mg [SD=26.51] p=0.021) and continued to significantly increase through day 22 (81.90 mg [SD=32.80]; p=0.004). Between day 15 and day 22, the MDD of gabapentin in the combination group significantly increased from 862.50 mg (SD=282.56) to 993.75 mg (SD=279.33) (p<0.001).

As show in **Table 12**, overall pain intensity significantly decreased from baseline to day 8 (p<0.001) with CRO monotherapy. The mean pain intensity continued to significantly decrease from day 8 to day 15 (p=0.004) but did not significantly further decrease by day 22 in the CRO group. Mean pain intensity scores also significantly improved with OG therapy by day 15 (p<0.001), followed by mild but not significant reductions at day 22.

#### Table 12. Changes in Mean Pain Intensity Throughout the Study Period

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Day** | **Overall Pain Intensity(n=53)** | **P value** | **CRO (n=21)** | **P value** | **OG (n=32)** | **P value** |
| Baseline (SD) | 7.91 (1.29) |  | 7.81 (1.25) |  | 7.97 (1.33) |  |
| Day 8 (SD) | 3.74 (1.11) | <0.001 | 2.62 (0.59) | <0.001 | 4.47 (0.67) | <0.001 |
| Day 15 (SD) |  |  | 2.00 (0.71) | 0.004 | 2.94 (0.67) | <0.001 |
| Day 22 (SD) |  |  | 1.91 (0.44) | 0.54 | 2.75 (0.76) | 0.14 |

Of the 63 patients enrolled, two patients were lost to follow up in phase I, resulting in 61 patients evaluable for the safety analysis. In phase I, three patients discontinued CRO therapy due to intolerable AEs. In phase II,

one additional patient was lost to follow up, and of the remaining 57 patients, 4 patients withdrew due to intolerable AEs (n=1, CRO vs. n=3, OG). No severe AEs were observed, and the most common side effect associated with CRO monotherapy was constipation, reported by 13.64% patients, while constipation and nausea were most commonly reported with OG therapy (14.26% and 8.57%, respectively). Other AEs reported in either group included vomiting, dizziness, sedation, sweating, pruritus, dry mouth, asthenia, and ataxia.

Ferrares F, Becchimanzi G, Bernardo M, et al. Pain treatment with high-dose, controlled-release oxycodone: an Italian perspective. *Ther Clin Risk Manag*. 2008;4(4):665-671.

Location: 10 centers in Italy; Study Dates: Apr 2007-Jun 2007

A 3-month, open-label, multicenter, observation study investigated the use and tolerability of high-dose controlled-release oxycodone (CRO) for the treatment cancer and noncancer pain.

Patients (age, >18 years) with a baseline pain intensity score >4 per numerical rating scale (NRS, 0-10) and were able to take oral medication were included. Patients who were undergoing current radiotherapy treatment, required modification of adjuvant medications, or had an intolerance to oxycodone were excluded. Existing pain management therapy was discontinued when eligible patients reported uncontrolled pain (defined as NRS>4), and patients were converted to CRO monotherapy. Initial CRO doses were individualized to each patient and titrated over a 3-to-4-day period until adequate pain control was achieved (defined as NRS≤2.9).

Pain scores per NRS were evaluated, and adverse events were monitored.

During the 3-month study period, 227 adult patients (mean age, 63.76 years; 137 males, 90 females) with cancer (n=207) and noncancer pain (n=20) were switched to CRO and monitored for at least 21 days.

Approximately 42% of patients were converted from low-dose oxycodone (<80 mg/day; oxycodone/APAP or CRO), transdermal fentanyl (30.0%), morphine (12.8%), transdermal buprenorphine (5.3%), weak opioids (6.2%), and NSAIDS (1.3%). At baseline, 47.98% of patients reported being in pain for ≤ 3 months, 32.83% for 3–6 months, and 19.19% for ≥6 months. The overall NRS calculated for participants at the outset of the study was 7.73. In total, 198 patients were evaluated, and pain control was attained with a mean daily CRO dose of CR 221.84 mg. Patients were treated with CRO for a mean duration of 37.24 days. With CRO therapy, the mean NRS score significantly improved from baseline to study end (7.73 vs. 2.85, p<0.00001). Adverse events, including constipation, nausea, and vomiting, were reported by 39.64% of patients, but did not result in study discontinuation.

Bercovitch M, Adunsky A. High dose controlled-release oxycodone in hospice care. *J Pain Palliat Care Pharmacother*. 2006;20(4):33-39.

Study Dates: Two-year period beginning in 2001

A 2-year, retrospective, parallel group study evaluated the efficacy of high-dose OxyContin (>150 mg/day) in end-stage cancer patients in an inpatient hospice setting compared to those using lower doses of OxyContin.

Eligible patients were categorized based on their maximum daily doses of OxyContin received during hospitalization: low (0-30 mg), moderate (31-150 mg), and high (>150 mg). This categorization was based on an oxycodone to morphine conversion ratio of 2:1. Pain intensity was rated using the visual analog scale (VAS) and/or numerical rating scale (NRS), and the combined scores were categorized into a 5-level scale: no pain, low (VAS/NRS=1-3), moderate (VAS/NRS=3-6), severe (VAS/NRS=6-8) and excruciating (VAS/NRS=8-10).

Additional data, including pain type and use of rescue analgesia, were collected using the Multidimensional Continuous Pain Assessment Chart. Quality of life was assessed by the Karnofsky scale (above 40, or less; the lower the score, the worse the survival), mood was evaluated using a questionnaire (0=stupor/inability to determine, 1=deeply sad/depressed, 2=sad/depressed, 3=normal), and sleep quality assessed using a 4-point scale (0=does not sleep at all, 1=wakes up frequently, 2=infrequent wake-ups, 3=normal sleep). Quality of life evolution in each of these aspects was analyzed as a function of time, i.e., sleeping well at least half of the time, maintaining a Karnofsky score over 40 at least half of the time, maintaining a good mood for at least 25% of the time. Adverse events were also monitored.

Ninety-seven consecutive patients (mean age, 73.3±12.8 years; 44 males, 53 females) were treated with OxyContin. The mean daily doses of OxyContin per group are presented in **Table 13**. There was no association between demographic parameters, including age, and OxyContin doses or mean survival of OxyContin treated patients amongst the three dose groups. Painful bony metastases were significantly correlated with high doses of OxyContin (p=0.008). The degree of pain was significantly correlated with being in the higher dose group (p=0.039). The use of rescue medication was limited in all three dose groups (9%, low-dose vs. 12%, moderate-dose vs. 10%, high-dose). No significant differences in sleep quality or mood were observed. For at least half of the study duration, patients in the moderate- and high-dose groups maintained Karnofsky scores >40 points (OR=3.77, CI 1.1-13.0 and OR=4.95, CI 0.8-29.9, respectively).

There were no significant differences in the adverse events regarding anorexia, somnolence, nausea, vomiting or constipation amongst the three groups aside from dry mouth, which was reported more frequently by patients receiving low-dose OxyContin (p=0.014).

#### Table 13. Mean Daily Doses of OxyContin in Terminal Cancer Patients

|  |  |  |
| --- | --- | --- |
| **OxyContin Treatment Group** | **Number of Patients (%) N=97** | **Mean Daily Dose of OxyContin (mg)** |
| Low-dose (<30 mg/day) | 34 (35%) | 19.4±1.4 |
| Moderate-dose (31-150 mg/day) | 45 (46%) | 62.2±28.3 |
| High-dose (>150 mg/day) | 18 (19%) | 231±74.9 |

Mucci-LoRusso P, Berman BS, Silberstein PT, et al. Controlled-release oxycodone compared with controlled- release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *Eur J Pain.* 1998;2(3):239-249.

Location: 9 centers in US; Study Dates: Jun 1994-Dec 1995

The safety and efficacy of OxyContin was compared to MS Contin in a multi-center, randomized, double-blind, double-dummy, parallel group study in adult cancer patients who required around-the-clock treatment with opioid analgesics for chronic cancer-related pain.

Patients who required the equivalent of 30 mg to 340 mg of oral oxycodone daily, or patients on maximally labeled doses of non-opioid analgesics who, in the investigator’s judgment, would require at least 30 mg oral oxycodone daily, were considered eligible for inclusion in the study. Patients having a history of sensitivity to oxycodone or morphine, any contraindications for opioid therapy, or severely compromised organ function were excluded from the study. Patients were randomly assigned to treatment with OxyContin or MS Contin (both q12h) for up to 12 days. The initial daily dose for each patient was calculated based on the patient’s pre- study daily opioid use, using standard conversion factors. The dose was titrated upward until stable pain control was achieved. Stable pain control was achieved if over a 48-hour period the dose was unchanged, no more than two supplemental analgesic doses were taken in each 24-hour period, the dosing regimens for any non-opioid analgesics or adjuvants were unchanged, the patient reported acceptable pain control, and any adverse events were tolerable. The supplemental analgesic was immediate-release (IR) oxycodone in the OxyContin group and IR morphine in the MS Contin group.

Pain intensity was assessed at baseline and before each q12h dose using a categorical scale (0=none, 1=slight, 2=moderate, 3=severe); acceptability of therapy and quality of life were each assessed at baseline and at the end of the study. A categorical scale (1=very poor, 2=poor, 3=fair, 4=good, 5=excellent) was used to assess acceptability of therapy, and the Functional Assessment of Cancer Therapy – General (FACT-G) was used to assess quality of life. Pharmacokinetic, pharmacodynamic, and safety evaluations were also completed. Power calculations indicated that 80 patients (40 in each treatment group) would be adequate to detect a 20% difference in mean pain intensity scores with 80% power and 5% significance level.

Of the 101 patients enrolled, 100 patients received at least one dose of study medication (n=48, OxyContin and n=52, MS Contin). The mean final daily dose following titration was 101 mg (range, 40 mg-360 mg) for OxyContin and 140 mg (range, 60 mg-300 mg) for MS Contin. The percentage of patients achieving stable analgesia was 83% (n=40) with OxyContin and 81% (n=42) with MS Contin, and the median time to achieve stable pain control was 2 days in each treatment group. Pain was well controlled during the study in both treatment groups, with no significant differences between treatments. During the last day of the study for each patient, mean pain intensity significantly improved (p≤0.005) in both groups from baseline (1.9 to 1.3, OxyContin; 1.6 to 1.0, MS Contin), but was not significantly different between the treatments.

Compliance with therapy was good in both groups, with 83% of the patients in each group taking all of their scheduled q12h doses. Mean acceptability of therapy improved significantly from baseline in both treatment groups, from 3.1 to 4.0 in the OxyContin group (p=0.0001) and 3.3 to 3.9 in the MS Contin group (p=0.0061). Both treatment groups rated therapy as good to excellent at the end of the study, with no differences between treatments. Quality of life, assessed by FACT-G questionnaire, showed no clinically significant changes during the study in either group.

Seventy-nine of 100 patients reported at least one adverse event during the study: 40 (83%) patients in the OxyContin group and 39 (75%) in the MS Contin group. The most common types of adverse events reported were typical opioid side effects. Hallucinations were reported by two patients in the MS Contin group and no patients in the OxyContin group. Overall, the adverse events were similar in the OxyContin and MS Contin groups. While spontaneous reports of pruritus were similar in the two treatment groups, elicited scores for “itchy” (rated by patients) and “scratching” (rated by observers) at 3 hours after dosing were lower in the OxyContin group than in the MS Contin group (p0.044).

Kaplan R, Parris WCV, Citron ML, et al. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *J Clin Oncol*. 1998;16(10):3230-3237.

Location: 17 centers in US; Study Dates: Jan 1992-Jan 1994

A double-blind, repeated-dose, parallel group study evaluated the safety and efficacy of OxyContin versus immediate-release (IR) oxycodone in patients with chronic cancer pain who were being treated with a strong single-entity opioid or ≥10 tablets per day of a fixed combination opioid/non-opioid analgesic.

Male and female patients with cancer-related pain whose pain had been managed with a stable dose of a single-entity opioid or fixed-dose opioid/non-opioid (≥10 tablets/day) and had stable co-exist disease were eligible to participate. Originally, patients were excluded if they had been receiving any analgesics or if they received radiotherapy prior to enrollment or during the study period, but these parameters were eliminated to facilitate enrollment.

Eligible patients were randomized to double-blind treatment with OxyContin 10 mg every 12 hour or IR oxycodone 5 mg four times per day. Dose titration or supplemental analgesic use for breakthrough pain was not allowed in the initial study protocol. However, following an interim analysis after the enrollment of 108 patients, the study protocol was amended to include open-label titration with IR oxycodone before patients were randomized to double-blind treatment. Supplemental analgesia with 5 mg IR oxycodone was also permitted for the rest of the study.

The initial daily oxycodone dose for each patient was calculated based on the patient’s pre-study opioid dose, using standard conversion factors. Primary efficacy variables were mean pain intensity and mean acceptability of therapy. Patients rated their pain intensity at baseline and four times each day during the study period using a categorical verbal rating scale (0=none, 1=slight, 2=moderate, 3=severe). Acceptability of therapy was rated at baseline and twice daily using a five-point categorical rating scale (1=very poor, 2=poor, 3= fair, 4=good, 5=excellent). Pharmacokinetic, pharmacodynamic, and safety evaluations were also completed.

A total of 164 patients were randomized to double-blind treatment. The mean daily doses prior to protocol amendment averaged 114 mg (range, 20 mg-400 mg) for OxyContin and 127 mg (range, 40 mg-640 mg) for IR oxycodone. After the protocol was amended, the mean daily doses averaged 123 mg (range, 20 mg-360 mg) for OxyContin and 137 mg (range, 40 mg-600 mg) for IR oxycodone. Mean pain intensity scores were slight at baseline and on each study day with no clinically significant differences between treatment groups. In addition, no significant differences between the groups emerged for pain intensity by time of day. Overall mean 5-day pain intensity was also slight in both groups, with mean scores of 1.3±0.1 for both OxyContin and IR oxycodone (no significant difference between treatment groups). Mean ratings for acceptability of therapy did not differ significantly between groups during each of the 5 study days or during the daytime and overnight.

Compliance was good in both treatment groups, with 93% of all enrolled patients taking all doses and 96% taking ≥90% of doses of study medication.

Significantly fewer adverse events occurred with OxyContin than with IR oxycodone (109 vs. 186, respectively; p=0.006). Adverse events were consistent with those reported for opioids in cancer patients, and most commonly involved the gastrointestinal or nervous systems. Significantly fewer gastrointestinal adverse events occurred in the OxyContin group compared to the IR oxycodone group (p=0.02). Also, fewer patients in the OxyContin group reported headache compared with the IR oxycodone group (p=0.029). Adverse events required discontinuation of treatment in six patients in the OxyContin group and ten in the IR oxycodone group during double-blind treatment, with gastrointestinal complaints being the most common reason for discontinuation.

Citron ML, Kaplan R, Parris WCV, et al. Long-term administration of controlled-release oxycodone tablets for the treatment of cancer pain. *Cancer Invest.* 1998;16(8):562-571.

Location: 13 centers in US; Study Dates: Dec 1982-Mar 1994

Patients who had participated in one of two double-blind studies (Parris et al., 1998; Kaplan et al., 1998) comparing the efficacy and safety of OxyContin and immediate-release (IR) oxycodone over a period of 5 days were invited to participate in an open-label, multi-center, 3-month study of the safety and efficacy of OxyContin tablets administered chronically to patients with cancer-related pain in a usual care clinical setting. The Parris et al., study included patients previously treated with 6-9 tablets of a fixed opioid/non-opioid combination analgesic (low-dose group), and no titrations to analgesic effect or supplemental analgesia were allowed. The Kaplan et al. study, on the other hand, included patients previously treated with a single-entity strong opioid or a high dose (>9 tablets) of fixed combination analgesics (high-dose group).

A total of 87 patients (n=30, Parris et al. and n=57, Kaplan et al.) were included in the study. Patients who had hypersensitivity to oxycodone, paralytic ileus, or severely compromised organ function were excluded from the study. Patients who had a history of adverse reactions to opioids and certain centrally-acting drugs or cimetidine were also excluded if they needed treatment with both an opioid and either of these two medications. OxyContin tablets were administered every 12 hours starting at doses determined by the patient’s daily opioid requirements at study entry. Dose titration and management of breakthrough or incident pain with IR oxycodone were allowed. An increase in the OxyContin dose was indicated when the patient’s pain intensity was greater than slight, breakthrough pain occurred regularly at the end of the 12-hour dosing interval, and more than two rescue doses were required in a 24-hour period. Although non-opioid analgesics were not allowed initially, a protocol amendment allowed their use if patients were taking these medications on a regular schedule at study entry. The primary endpoints of the study were pain intensity and acceptability of therapy. Every week, patients evaluated pain intensity using a 4-point categorical scale (1=none, 2=slight, 3=moderate, 4=severe) and acceptability of therapy using a 5-point scale (1=very poor, 2=poor, 3=fair, 4=good, 5=excellent). Pharmacokinetic, pharmacodynamic, and safety assessments were also performed.

Among the patients who took study medication, pain intensity and acceptability of OxyContin therapy remained stable throughout the study. Weekly pain intensity scores were slight to moderate throughout the study period. The overall weekly pain intensity score (1.6±0.1) was comparable to that at study entry (1.5±0.1). There were no significant differences in weekly, baseline, or overall mean pain intensity scores between the low-dose and high-dose study groups. Weekly acceptability of therapy scores were fair to good throughout the study period. The overall weekly acceptability of therapy scores (3.4±0.1) were comparable to that at study entry (3.5±0.1).

The overall mean total daily dose of OxyContin was 112.7±11.1 mg. The mean daily dosage of OxyContin tablets increased over the 12-week study, from 58.6±3.7 mg to 89.6±11.1 mg among patients (n=28) who had been in the low-dose, double-blind study group, and from 126.5±16.4 mg to 158.6±20.5 mg among patients (n=51) who had been in the high-dose, double-blind study group. Overall, the mean increase in daily dosage was approximately 30 mg for both groups (p=0.0001). The substantial difference in the dosages used in the two double-blind studies was due to the type of patients allowed in each study. Sixty-five percent of all rescue medication was used during the day, especially between noon and 4 p.m., a period that probably reflects increased activity of patients. There was no increase in use of rescue medication at the end of the dosing interval, supporting the twice-daily (q12h) dosing regimen for OxyContin tablets. Ninety-three percent of the patients were at least 90% compliant; 59% took all scheduled doses.

For those patients who completed all 12 weeks of the study, there was a significant decrease in the number of patients with opioid-related adverse events over time (55%, week 1 vs. 13%, week 12; p=0.0002), while stable pain control was maintained. Incidence of constipation decreased from 30% to 10% (p=0.043) and nausea from 22.5% to 2.5% (p=0.013). The dose of OxyContin was titrated up or down in 66 patients (84%) at least once during the 12-week study period. Increased or uncontrolled pain was the major reason for dose increase. A total of 13 patients (15%) discontinued the study due to adverse events.

#### Studies in Patients with Osteoarthritis-related Pain

Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig*. 2010;30(8):489-505.

Location: 87 study centers in the US, 15 in Canada, 6 in New Zealand, and 4 in Australia, Study Dates: Feb 2007-Jun 2008

This multicenter, international, randomized, double-blind, active- and placebo-controlled, parallel arm, phase III study compared the efficacy and tolerability of tapentadol extended-release (TER) and oxycodone controlled- release (OCR) for the management of moderate to severe chronic osteoarthritis (OA) pain of the knee.

Male and female patients (age, ≥40 years) with a diagnosis of OA of the knee per American College of Rheumatology criteria, functional capacity I-III, pain at the reference joint necessitating the use of non-opioids or opioids at doses ≤160 mg oral morphine/day for ≥3 months prior to screening, and a pain intensity score ≥5 during the three days preceding randomization per 11-point numerical rating scale (NRS) were eligible to participate in the study.

The study consisted of five periods: screening (≤14 days), washout (3-7 days), titration (3 weeks), and maintenance (12 weeks), and follow-up (14 days after last dose of study medication). The double-blind period included the titration and maintenance phases. After washout, patients were randomized to initial doses of twice daily TER 50 mg, OCR 10 mg, or placebo. After three days, doses could be increased to TER 100 mg or OCR 20 mg twice daily, which were the minimum doses for the remainder of the study. At 3-day intervals, doses could be increased by twice-daily TER 50 mg or OCR 10 mg, to a maximum dose of twice-daily TER 250 mg or OCR 50 mg. No additional analgesic medication was allowed during the maintenance period, with the exception of paracetamol ≤1000 mg/day for up to 3 days and for relief of pain unrelated to the OA pain.

In the US, the primary endpoint was change from baseline in average pain intensity per NRS (0=no pain, 10=pain as bad as you can imagine) at week 12 of the maintenance period, while the ex-US primary endpoint was change from baseline in average pain intensity per NRS over the entire 12-week maintenance period.

Adverse events (AEs), including treatment-emergent adverse events (TEAEs) were monitored throughout the study and 10-14 days after the last administration of study medication. The Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire was administered at baseline and end of study treatment. The clinician- rated Clinical Opiate Withdrawal Scale (COWS) was administered after cessation of therapy, and the patient- rated Subjective Opiate Withdrawal Scale (SOWS) was administered to patients in US sites during the 4 days after cessation of therapy.

A total of 1030 patients were randomized, but 67 patients did not receive study medication and 1 was erroneously enrolled twice, resulting in 1023 patients in the intent-to-treat (ITT) population (n=344, TER; n=342, OCR; n=337, placebo). The mean (SD) total daily dose (TDD) for TER and OCR over the 15-week double-blind phase was 299.3 (107.16) mg and 48.2 mg (23.94), respectively. Both treatments resulted in significant reduction in average pain intensity compared to placebo during the overall maintenance period (oxycodone CR LSM difference vs. placebo, -0.3; 95% CI [-0.67, 0.00]; TER LSM difference vs. placebo, -0.7 [- 1.00, -0.33]); however, there was no significant change in average pain intensity with OCR at week 12.

The incidence of TEAEs was 61.1% (206/337) with placebo, 75.9% (261/344) with TER, and 87.4% (299/342) with OCR. The most common (≥10%)TEAEs reported in either of the active treatments were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue, and pruritus. Constipation as well as nausea and/or vomiting were reported significantly less by patients taking TER compared to those taking OCR (p<0.001). TEAEs, most commonly GI-related, lead to discontinuation of in 19.2% (66/344), 42.7% (146/342), and 6.5% (22/337) of patients in the TER, OCR, and placebo groups, respectively. Twenty patients experienced serious AEs during the double-blind treatment phase and within 30 days of treatment cessation (n=4, TER; n=10, OCR; n=6, placebo). One patient, with a history of morbid obesity, died due to a myocardial

infarction that occurred 90 days after receiving the first dose of OCR, and the death was deemed unrelated to study medication by the investigator.

When comparing overall PAC-SYM scores, the LSM change from baseline was significantly lower with TER than with OCR (p<0.001). COWS scores for patients who did not use opioids following discontinuation of study medication indicated that patients in all treatments had no, mild or moderate opioid withdrawal. In patients administered the SOWS, there was reportedly no significant difference in scores between tapentadol and placebo.

Markenson JA, Croft J, Zhang PG, Richards P. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clin J Pain*. 2005;21(6):524-535.

Location: 9 centers in US; Study Dates: Jun 1997-Aug 1996

A 90-day, double-blind, randomized, placebo-controlled, parallel-group study evaluated functional outcomes, as well as efficacy and safety, of OxyContin given q12h compared to placebo in patients with persistent moderate to severe osteoarthritis (OA) pain, uncontrolled by standard therapy (nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen [APAP], and/or short-acting opioids).

Eligible patients had to have OA, as defined by the American College of Rheumatology guidelines, had to have been taking NSAIDs or APAP at a therapeutic and/or tolerated (but not as necessary) dose for at least 2 weeks before day 0, were not taking NSAIDs because they were NSAID-intolerant or at high risk for toxicity or complications, or were receiving as necessary oral opioid therapy that was equivalent to ≤60 mg of oxycodone per day (with or without NSAIDs or APAP analgesia). Patients were excluded if they were allergic to opioids, were scheduled to have surgery during the study period, had unstable coexisting disease or active dysfunction, had active cancer, were pregnant or nursing, had a past or present history of substance abuse, were involved in litigation related to their pain, or had intra-articular or intramuscular steroid injections involving the joint or site under evaluation within 6 weeks prior to baseline.

Patients who met entry criteria were randomly assigned to receive either OxyContin 10 mg or matching placebo q12h. Patients were permitted to continue their stable NSAID or APAP regimen during the study. Patients were not permitted to continue receiving prestudy short- or long-acting opioids. Initial titration to stable dosing was the point at which the patient achieved an average pain intensity score of ≤4 for a 48-hour period on the same dose. The dose of study drug could be adjusted at ≥24-hour intervals at any time during the study, and asymmetric morning and evening dosing was allowed. The dose of OxyContin could be increased to a maximum of 60 mg q12h or decreased depending on pain intensity or adverse events.

Primary efficacy variables were Brief Pain Inventory (BPI) average pain intensity scores (scale from 0 to 10) at completion of initial titration, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at days 30 and 60, and the percentage of patients discontinuing due to inadequate pain control. Secondary efficacy variables included BPI score at each visit and acceptability of pain medication.

One hundred seven patients (ages, 38-89 years; mean age, 63 years) received either OxyContin (n=56) or placebo (n=51) and were included in the intent-to-treat analysis. From day 30 until the end of the study, the average OxyContin dose remained stable at 57 mg/day. Average pain intensity at stable dosing was significantly lower in the OxyContin group compared to placebo (5.1±0.3 vs. 6.0±0.3; p=0.042). The WOMAC Index scores for pain (p=0.001), stiffness (p<0.001), and physical function (p<0.001), as well as the composite score (p<0.001), were significantly lower with OxyContin than with placebo at visits 3 (day 30) and 5 (day 60). The BPI scores showed significantly decreased pain intensity, increased pain relief, and less pain interference with function in the OxyContin group compared to the placebo group at all of the treatment visits. Thirty-four (67%) patients in the placebo group discontinued due to inadequate pain control compared with nine (16%) in the OxyContin group (p<0.001). At the final visit (day 90), patients receiving OxyContin were more satisfied with their pain medication than patients receiving placebo (p<0.001).

The most common adverse events reported during the study for OxyContin were constipation, nausea, dizziness, somnolence, pruritus, headache, diarrhea, vomiting and sweating.

Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Arch Intern Med*. 2000;160(6):853- 860.

Location: 7 centers in US; Study Dates: Jun 1993-Mar 1995

A two-week, double-blind, randomized, placebo-controlled, repeated-dose, parallel group study evaluated the safety and efficacy of two fixed doses (10 mg or 20 mg) of OxyContin or placebo, given q12h in patients with moderate to severe pain due to osteoarthritis. Patients participating in the placebo-controlled trial were eligible to participate in a 6-month extension trial with the option to participate in two additional 6-month extensions.

Patients, ≥18 years of age, with a confirmed diagnosis of osteoarthritis (based on pre-defined clinical and radiographic criteria) and experiencing frequent or persistent pain for at least one month and whose average current daily pain intensity was moderate or greater were enrolled in the study. Use of NSAIDs during the study was permitted if the dose had been stable for at least one month prior to the study. No dose titration or supplemental analgesics were allowed.

The primary efficacy endpoint was mean pain intensity calculated from patients’ daily categorical score. Pain intensity was evaluated at baseline (Day 0) and four times each day during the study (morning [assessing night pain], mid-day [assessing morning pain], evening [assessing afternoon pain], and bedtime [assessing evening pain]) using a 4- point categorical scale (0=none, 1=mild, 2=moderate, and 3=severe). Secondary endpoints of quality of sleep (1=very poor, 2=poor, 3=fair, 4=good, 5=excellent), acceptability of therapy (1=very poor, 2=poor, 3=fair, 4=good, 5=excellent), and number of awakenings per night due to pain were also evaluated. Additionally, patients completed a modified version of the Stanford Health Assessment Questionnaire, the Activities and Lifestyles Questionnaire (ALQ), and the Brief Pain Inventory Questionnaire (BPI) at baseline, week 1, and week 2. Adverse events (AEs) reported by patients or observed by the investigators were also recorded and analyzed.

Patients (N=133; mean age, 62 years; age range, 32-90 years) were randomized to placebo (n=45), 10 mg of OxyContin (n=44), or 20 mg of OxyContin (n=44). The 20 mg dose of OxyContin was found to be significantly more effective than placebo and 10 mg OxyContin in reducing mean pain intensity at weeks 1, 2, and overall during the study (p<0.05). Overall mean pain scores showed little difference in night, morning, afternoon, or evening pain assessments, demonstrating continuous analgesia over 24 hours. At weeks 1 and 2, based on the BPI assessments of pain, the 20 mg OxyContin group was significantly more effective than placebo (p<0.5) in improving pain from baseline for pain right now and for worst and average pain in the last 24 hours.

The OxyContin 20 mg q12h group showed significant mean improvements (i.e., reductions) from baseline in interference of pain on mood, sleep, and enjoyment of life (p<0.05). The interference of pain on walking ability, general activity, normal work, and relations with others showed some improvement from baseline, but did not reach statistical difference. Treatment with OxyContin 10 mg or 20 mg q12h did not increase impairment of or improve performance of daily life functions, as measured with a standard instrument, the Stanford Health Assessment Questionnaire. Quality of sleep was significantly better in patients receiving OxyContin 20 mg q12h than in those receiving placebo at Week 1 and overall (p<0.05).

Significantly fewer patients discontinued the study due to ineffective treatment in the OxyContin 20 mg (n=5) and OxyContin 10 mg groups (n=12) than in the placebo group (n=22). Significantly more patients discontinued due to adverse events in the active groups than in the placebo group (n=12, OxyContin 10 mg; n=14, OxyContin 20 mg; n=2, placebo). Eighty-seven (65.4%) patients reported at least one treatment-related AE during the study, and those occurring in ≥10% of patients are presented in **Table 14**. No AEs were deemed to be life-threatening.

#### Table 14. Treatment-related AEs Reported by ≥10% of Patients During the Placebo-Controlled Trial

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment-related Adverse Event** | **Number of Patients (%)** | | |
| **Placebo n = 45** | **OxyContin 10 mg q12h n = 44** | **OxyContin 20 mg q12h n = 44** |
| Nausea | 5 (11) | 12 (27) | 18 (41) |
| Constipation | 3 (7) | 10 (23) | 14 (32) |
| Somnolence | 2 (4) | 11 (25) | 12 (27) |
| Vomiting | 3 (7) | 5 (11) | 10 (23) |
| Dizziness | 4 (9) | 13 (30) | 9 (20) |
| Pruritus | 1 (2) | 8 (18) | 7 (16) |
| Headache | 3 (7) | 4 (9) | 5 (11) |

Open-Label Extension

Similar to the placebo-controlled trial, patients enrolled in the extension phase rated their pain intensity using a 4-point categorical scale (0=none, 1=slight, 2=moderate, 3=severe), rated quality of sleep using a 5-point scale (1=very poor, 5=excellent), recorded the number of nocturnal awakenings, and completed an activity and lifestyle questionnaire. Adverse events (AEs) reported by patients or observed by the investigators were also recorded and analyzed.

Of the 133 eligible, 106 patients enrolled in the extension phase. Those who had received placebo or OxyContin 10 mg every 12 hours began the extension trial with a 10 mg OxyContin dose. Those previously randomized to 20 mg every 12 hours began the extension trial on that dose. OxyContin titration was permitted to balance adequate pain control with tolerable side effects. Asymmetric dosing was allowed, but all OxyContin dosing was every 12 hours. Patients could continue the use of NSAIDs, if on a stable dose, but the use of other analgesics was prohibited throughout the extension study. Continued need for opioid analgesia was assessed by scheduling respites from opioid therapy at weeks 4, 8, 16, 24, 48, and 64.

Fifty-eight patients completed 6 months of treatment, 41 completed 12 months, and 15 completed 18 months. The mean (SE) dose of OxyContin became constant at approximately 40 (2) mg/day by month 4, ranging from 39 (2) to 41 (4) mg/day between months 4 and 18. The greatest need for OxyContin titration occurred at week 2, and as the trial continued, a higher percentage of patients required downward titration.

Throughout the trial, pain intensity was controlled below a “moderate” level, with mean (SE) pain intensity of

1.7 (0.1) out a possible 3 at month 6. During months 8 and 18, mean (SE) pain intensity ranged from 1.7 (0.1) to 1.9 (0.1). At the end of each scheduled respite, mean pain intensity scores increased above “moderate” (range, 2.3 to 2.5). These scores were close to those at entry into the controlled trial preceding the extension, supporting a continued need for opioid analgesia in these patients.

Quality of sleep improved and the number of pain-related nocturnal awakenings decreased during the long- term study. Mean (SE) quality of sleep was rated as “fair” (3.1 [0.1]) at extension-study entry and improved to “good” (3.6 [0.1]) at six months and remained in the range of 3.4 (0.2) to 3.7 (0.1) for the rest of the extension phase of the trial. The mean (SE) number of night awakenings was 1.6 (0.2) at entry into the extension phase,

0.7 (0.1) at month 6, and ranged from 0.6 (0.2) to 1.4 (0.3) for the remainder of participation.

An activity and lifestyle questionnaire administered at baseline found that patients were not highly functionally- impaired when they entered the long-term trial. Patients reported the ability to perform activities of daily living “without any difficulty” or “with some difficulty.” Reassessment at month 6 and throughout the remainder of the trial did not suggest that OxyContin therapy led to either deterioration or improvement in function.

Sixty patients (56.6%) discontinued participation in the study, most often due to adverse events (n=32). AEs occurring in ≥10% of patients are presented in **Table 15** Throughout the trial, the duration of nausea, pruritus, somnolence, and constipation decreased significantly (p<0.001). Thirteen patients were hospitalized. In eight, the hospitalization was judged unrelated to OxyContin. In five, though the reason for hospitalization resolved without treatment, the contributory effect of OxyContin was likely (abdominal pain [n=2], constipation [n=1],

withdrawal syndrome [n=1], confusion and fall [n=1]). The patient with confusion was on a stable OxyContin dose, but was receiving many CNS-active medications; the disorientation was attributed to the doubling of the patient’s flurazepam dose. The patient hospitalized for withdrawal syndrome had completed the study on the previous day with a daily OxyContin dose of 70 mg; the withdrawal symptoms resolved after three days.

Another patient, on a daily dose of 60 mg, experienced withdrawal symptoms after running out of study medication. The patient had not reported withdrawal symptoms during scheduled respites from doses of 30 or 40 mg/day. Adverse experiences reported by more than 10% of patients during the scheduled respites were nervousness (n=9) and insomnia (n=8). A small number of participants reported some other symptoms that are consistent with acute withdrawal following abrupt cessation of OxyContin therapy (Data on File).

#### Table 15. AEs Reported by >10% of Patients in the Extension Trial

|  |  |
| --- | --- |
| **Treatment-related Adverse Event** | **Number of Patients** |
| Constipation | 55 |
| Somnolence | 32 |
| Nausea | 25 |
| Pruritus | 21 |
| Nervousness | 16 |
| Headache | 14 |
| Insomnia | 14 |

Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol*. 1999;26(4):862-869.

Location: 9 centers in US; Study Dates: Nov 1995-Oct 1996

A double-blind, randomized, multi-center placebo-controlled trial compared the efficacy and safety of OxyContin q12h, immediate-release (IR) oxycodone-acetaminophen (APAP) tablets four times daily (QID), and placebo for patients with moderate to severe osteoarthritis (OA) pain.

Patients eligible for the study were adults with moderate to severe average daily OA pain despite regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) at stable doses that had been experiencing frequent or persistent pain for at least 1 month. The diagnosis of OA for these patients was confirmed by certain clinical and radiographic criteria. Patients excluded from the study were those who were involved in litigation related to their pain or injury; those patients who had received intraarticular steroid injections within 6 weeks of study entry if the injection involved the joint being evaluated; those patients with contraindications or allergies to acetaminophen, oxycodone, or other opioids; and those patients with active cancer, severe organ dysfunction, or history of substance abuse.

All patients continued NSAID therapy at stable prestudy dosages throughout the study. No other analgesics were permitted. Patients identified the joint at which the OA pain was most pronounced and this site was used for subsequent evaluations of pain intensity. Subjects first entered a 30-day, open-label titration phase, in which IR oxycodone-APAP tablets were administered QID, and the dose adjusted until pain intensity was less than moderate for several days in the absence of intolerable and unmanageable side effects. Dose titration was permitted up to a maximum of 60 mg daily (due to the limitations of maximum daily APAP of 4000 mg/day when patients were randomized to receive the fixed combination product). After the 30-day titration phase, patients were randomized to receive double-blind treatment for another 30 days with OxyContin, IR oxycodone-APAP, or placebo at the oxycodone dose established during titration. There was no washout period between the titration and double-blind phases. The primary efficacy endpoint was global pain intensity at the target joint which was rated using a categorical scale (0=none, 3=severe). Patients made global assessments at baseline, at the end of the 4-week titration phase, and after 2 and 4 weeks of double-blind treatment. Global quality of sleep was assessed as a secondary efficacy endpoint using a categorical scale (1=very poor, 5=excellent).

One hundred seven patients (ages, 29-81 years; mean age, 57 years) completed titration and were randomized to double-blind treatment, all of which were included in the intent-to-treat analysis (n=34, OxyContin; n=37, IR oxycodone/APAP; n=36, placebo). The sites most frequently identified for evaluation were the back and neck (49%) and the knee (37%). The mean oxycodone dose at the end of titration was about 40 mg/day. The mean dose was similar in patients later randomized to placebo (37.8 mg/day), OxyContin (39.9 mg/day), or IR oxycodone-APAP (40.3 mg/day). Mean global pain intensity after 2 and 4 weeks of double-blind treatment was significantly lower in the two active treatment groups than in the placebo group (p≤0.05). Mean global quality of sleep scores during double-blind treatment were significantly higher in each active treatment group when compared with the placebo group and remained significantly higher in the OxyContin group than in the IR oxycodone-APAP group (p=0.0382). Typical opioid side effects were the most frequent adverse events reported during both the titration and double blind phases: somnolence, constipation, nausea, pruritus, dizziness, dry mouth, and vomiting. Nausea and dry mouth were reported significantly less frequently with OxyContin than with IR oxycodone-APAP (p=0.03 and p=0.09, respectively).

#### Studies in Patients with Low-Back Pain

Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain*. 1999;15(3):179-183.

Location: 5 centers in US; Study Dates: Aug 1993-Jul 1994

A multi-center, randomized, double-blind, active-controlled, two-period, crossover study compared the efficacy and safety of OxyContin tablets with immediate-release (IR) oxycodone tablets in patients with persistent non- malignant moderate to severe back pain.

Patients were included in the study if they were ≥18 years of age, had stable chronic nonmalignant moderate to severe low back pain, and were receiving maximally effective doses of non-opioid analgesics with or without opioids. Patients were excluded if they had a history of substance abuse or were involved in litigation regarding their low back pain.

Patients were enrolled and randomized to an open-label titration phase with either OxyContin 10 mg q12h or IR oxycodone 5 mg four times daily until stable pain control was achieved for 48 hours. Stable pain control was defined as a pain intensity of ≤1.5 on a 4-point scale, minimal usage of supplemental analgesic (no more than two IR oxycodone doses per day), with a total daily oxycodone dose of ≤80 mg and minimal or no side effects. Patients who achieved stable pain control within 10 days were then randomized to the double-blind, two-arm crossover phase of the study. Each crossover period lasted for 4 to 7 days with no intervening washout period between treatments. The doses of OxyContin and IR oxycodone during the double-blind phase were those determined during the titration phase of the study. Patients rated pain intensity using a categorical scale (0=none, 1=slight, 2=moderate, and 3=severe) in the morning, afternoon, evening, and bedtime and also recorded data use of rescue medication in a daily dairy. Adverse events (AEs) were recorded at each contact during the study. The primary efficacy endpoint was pain intensity and secondary endpoints included number of rescue doses and number of patients successfully titrated to stable pain control.

Of 57 patients enrolled, 47 (82%) successfully completed the open-label titration phase and were randomized to double-blind treatment. Ninety-one percent of the patients were titrated to stable pain control, with no difference between formulations in the percentage of patients achieving pain control. Pain intensity decreased from "moderate to severe" (2.3±0.1) before the titration to "slight" by the end of titration and was maintained throughout the double-blind period. Overall pain intensity was 1.2±0.1 with OxyContin and 1.1±0.1 with IR oxycodone. Mean pain intensity was also slight at each daily assessment (morning, afternoon, evening, and bedtime) for both formulations. The average daily doses of OxyContin and IR oxycodone required to provide stable analgesia were similar (40 mg±4.2 mg vs. 38.5 mg±4.0 mg, respectively). Patients required 0.6 doses of supplemental analgesia per day, with no statistically significant difference between treatments.

Fifty-three patients (93%) reported an AE. Over 90% of the AEs were mild to moderate in severity and were similar between OxyContin and IR oxycodone. The overall incidence of AEs declined over the three phases of the study: from 89% during titration to 77% in period 1 and then to 62% in period 2. The most common AEs reported in the study were constipation, nausea, pruritus, somnolence, and dizziness. In general, the incidence of opioid-related AEs, except for constipation, decreased over time.

#### Studies in Patients with Pain associated with Diabetic Neuropathy

Yao P, Meng LX, Ma JM, et al. Sustained-release oxycodone tablets for moderate to severe painful diabetic peripheral neuropathy: A multicenter, open-labeled, postmarketing clinical observation. *Pain Med*. 2012;13(1):107-114.

Location: 12 study centers in China; Study Dates: Oct 2009-Dec 2010.

A multicenter, randomized, open-label study evaluated the efficacy and safety of OxyContin tablets in patients with severe diabetic peripheral neuropathy (DPN).

Adult patients (age, >40 years) with moderate to severe DPN, (defined as a numerical rating scale (NRS) average pain score ≥5 over the last 24 hours), history of pain for at least four weeks, and able to communicate with physicians were eligible to participate in the study. Patients excluded from the study included: treatment with long-acting opioid analgesic; any contraindications to OxyContin tablets as described in the Full Prescribing Information; allergy to oxycodone HCl; any violation of relevant Chinese regulations.

Opioid-naïve patients were initiated on OxyContin based on NRS pain scores (NRS=5-6, OxyContin 5 mg every 12 hours [strength not available in US]; NRS=7-0, OxyContin 10 mg every 12 hours). For patients who had been taking opioid analgesics, OxyContin dosage was determined by a conversion table. Upward dose titration (25-50% of the original dose) was permitted until stable pain control was achieved. The primary efficacy endpoint was change in pain intensity every week during the 6-week treatment. Adverse events were monitored.

In total, 80 patients met the inclusion criteria and participated in the 6-week study. Of the 80 patients, 26 patients did not complete the 6-week follow-up (n=7, discontinuation due to adequate pain relief; n=17, lost to follow-up; n=1, lack of efficacy; n=1, discontinuation due to an AE). In the 80 patients, the average daily dose of OxyContin was 16.63±7.79 mg at 1 week and about 20 mg after 2 weeks in most patients, with 3-5 of these patients requiring >30mg. Pain intensity scores significantly decreased from 6.8±1.4 to 2.8±1.6 after 1 week of treatment (p<0.01) and scores remained <3 through the end of treatment. Thirty-eight (47.5%) patients had AEs, and the main AEs included nausea (n=15), vomiting (n=4), constipation (n=20), dizziness (n=8), dry mouth (n=1), urine retention (n=1), and febrile reaction (n=1). No serious AEs, drug withdrawal syndrome, drug craving, or drug seeking behavior were reported.

Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology*. 2003;60(6):927-934.

Location: 15 centers in US; Study Dates: Jun 1999-Jun 2000

A multicenter, randomized, double-blind, placebo-controlled, parallel group study was conducted to evaluate the efficacy and safety of OxyContin versus placebo in patients with moderate to severe persistent pain associated with diabetic polyneuropathy for a treatment period of up to six weeks.

Patients included in the study had stable diabetes mellitus, a glycosylated hemoglobin (HbA1C) level of ≤11%, painful distal symmetrical polyneuropathy documented by neurologic evaluation, reported bilateral foot pain for more than half the day for at least three months prior to enrollment with an average pain intensity score of ≥5 on an 11-point numeric scale (0=no pain,10=pain as bad as you can imagine), and experienced at least moderate pain in the absence of any opioid analgesic for three days before receiving study treatment. Patients were excluded from participation if they had unstable or poorly controlled diabetes; chronic pain unrelated to diabetic neuropathy; a history of substance or alcohol abuse within the past 10 years; serum creatinine levels

≥2.5 mg/dL; hepatic dysfunction ≥3 times the upper limit of normal; a history of active cancer in the past 3 years; hypersensitivity to oxycodone or opioids; rapidly escalating pain or recent neurologic deficit within the previous month; a total of more than three doses per day of a short-acting opioid formulation in the preceding 2 weeks; treatment with any long-acting opioid formulation; autonomic neuropathy or gastrointestinal dysfunction that could compromise drug absorption or increase the risk from therapy; and a need for elective surgery involving preoperative or postoperative analgesics or anesthetics during the study period. Women who were pregnant or breast-feeding were also excluded.

All opioid therapy was discontinued at least three days before starting any study medication. An initial washout/screening phase of 3 to 7 days was followed by a 42-day, double-blind treatment phase where patients were randomized to receive OxyContin 10 mg (one tablet) or placebo q12h. Upward titration was allowed to occur every three days (by one tablet in the morning and one tablet in the evening) up to a maximum dose of 60 mg twice daily (6 tablets twice daily). No opioid rescue was allowed. Medications taken for diabetes control, adjuvant medications (eg, anticonvulsants and tricyclic antidepressants), and other nonopioid analgesics (eg, NSAIDs or APAP) were allowed to be continued as long as they were at the same stable prestudy dose. Treatment lasted for up to six weeks and at the end of the study a final one-week taper was optional. The primary efficacy variable was the average daily pain intensity during the past 24 hours obtained during the study period from days 28 to 42. Pain intensity was rated in a daily diary using an 11-point scale (0=no pain, 10=pain as bad as you can imagine). The daily diary also included 0 to 10 scales for current pain and worst pain, satisfaction with pain medication scale (1=not satisfied, 6=totally satisfied), and scale for sleep quality (0=poor sleep, 10=excellent sleep). Adverse events (AEs) were also monitored.

The intent-to-treat population consisted of 159 patients who were randomized to either OxyContin or placebo. The baseline average daily pain intensity was similar between the two treatment groups (6.9, OxyContin vs. 6.8, placebo). Overall average daily dose of OxyContin was 37±21 mg/day (range, 10 to 99 mg/day) and for placebo was 52±25 mg/day (range, 20 to 99 mg/day). OxyContin was significantly more effective than placebo for the primary efficacy variable, overall average daily pain intensity from days 28 to 42, where the least squares mean score was 4.1±0.3 for the OxyContin group and 5.3±0.3 for the placebo group (p=0.002). Analyses of the secondary efficacy variables of overall scores for average pain intensity from days 1 to 27, pain right now, worst pain, satisfaction with study drug, and sleep quality from days 1 to 42 were also statistically improved for the OxyContin group (p<0.02).

The incidence of AEs was greater in the OxyContin group than in the placebo group. The most commonly reported AEs (≥10%) in the OxyContin group were those usually associated with opioid use, such as constipation, somnolence, nausea, dizziness, pruritus, vomiting, dry mouth, and asthenia. Fourteen serious AEs were reported in the study, none of which were considered related to the study drug (OxyContin: n=5, death, flulike syndrome, hyperglycemia, hypoglycemia, and epistaxis; placebo: n=9, alcohol intoxication, ascites, chest pain, asthenia, nausea, diarrhea, vomiting, decreased body weight, and dyspnea).

Watson CPN, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer E. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain*. 2003;105(1-2):71-78.

Location: 2 centers in Canada; Study Dates: Apr 1999-Nov 2000

A randomized, double-blind, crossover study was conducted to compare the efficacy and safety of OxyContin versus active placebo (benztropine) in the management of at least moderate pain associated with symmetrical distal sensory neuropathy.

Patients were included in the study if they had diabetes mellitus with stable glycemic control, painful symmetrical distal sensory neuropathy, at least moderate pain in the lower extremities assessed at the screening visit on a five-point categorical scale (0=none, 4=excruciating), a medical history of moderate daily pain based on the patient’s recall over the previous three months, one or more symptoms of diabetic neuropathy, and signs of reduced sensation, strength or tendon reflexes not attributable to any other cause. Patients were excluded from the study if they had intolerance to oxycodone, a history of drug or alcohol abuse, or significant pain of alternate etiology.

Two to seven days prior to randomization, patients were discontinued from all opioid analgesics. Patients were randomized to a starting dose of either OxyContin 10 mg q12h or active placebo 0.25 mg and titrated every 2-7 days to a maximum of OxyContin 40 mg q12h or active placebo 1 mg q12h. After four weeks of therapy, or earlier if patients experienced inadequate pain relief at the highest tolerated dose either with OxyContin or placebo, patients were crossed over to the alternate therapy without washout. Patients were allowed to continue on stable doses of antidepressants, anticonvulsants, or non-opioid analgesics. Breakthrough pain was managed with 325-650 mg acetaminophen every 4-6 hours as needed.

For OxyContin, the number needed to treat (NNT) was defined as 1/(the proportion of patients successfully treated with active treatment minus the proportion of patients successfully treated with placebo), where successful treatment was defined as having at least moderate pain relief using a 6-point pain relief scale (0=pain worse, 5=complete relief). Primary measures of efficacy for the evaluable population were overall pain intensity as measured by daily visual analog scale (VAS; 0=no pain, 100=unbearable pain) and a 5-point categorical scale (0=no pain; 4=unbearable pain) and weekly VAS and categorical scores for steady, brief, and skin pain intensity. The primary measure of pain-related disability was assessed weekly using the categorical disability scale, Pain Disability Index (PDI), which consists of seven subscales each representing a different area of functioning. Secondary measures of efficacy were pain relief, health-related quality of life (QOL), and impact of pain on sleep. Pain relief was assessed using a six-point categorical scale (0=complete relief; 5=pain worse). The SF-36 health-related status outcome measure was administered at baseline, crossover, and at the end of the study. The Pain and Sleep Questionnaire, which consisted of eight items, was administered to assess the impact of pain on sleep. Patients and investigators evaluated the effectiveness of pain medication and patients rated their satisfaction with the medication. At the end of the study, patients and investigators completed treatment preference.

The evaluable population consisted of 36 patients (mean age, 63.0±9.4 years) who had completed at least one week of treatment and evaluation in each phase of the crossover study. Patients receiving at least one dose of study medication were included in the safety analysis (n=43). Analysis of treatment sequence revealed no significant carryover effect for the primary variables.

Baseline pain intensity was 67.0±14.9 (VAS) and 2.7±0.6 (categorical pain intensity). The mean daily dose for the last week of each treatment was 40.0±18.5 mg for OxyContin and 1.2±0.6 mg for benztropine (49.4±23.8 mg placebo). Compared to placebo, OxyContin resulted in significantly lower mean VAS pain intensity scores (21.8±20.7, OxyContin vs. 48.6±26.6, placebo; p=0.0001) and categorical pain intensity scores (1.2±0.8, OxyContin vs. 2.0±0.8, placebo; p=0.0001) as well as significantly better pain relief scores (1.7±1.3, OxyContin vs. 2.8±1.1 placebo; p0.0005) during the last week of treatment assessed in patients’ pain diaries. Steady, brief, and skin pain intensities were significantly reduced with OxyContin compared to placebo (p=0.0001 for all

measures). The overall pain and sleep scores were significantly better for OxyContin compared to placebo (p=0.0003).

All variables in the PDI were significantly better with OxyContin (family/home responsibilities, recreation, social activity, occupation, self-care, life-support activity, total pain and disability; p0.05), with the exception of sexual behavior. For the SF-36, OxyContin was significantly better than placebo in most health-related QOL domains, including Physical Functioning (p=0.0029), Pain Index (p=0.0001), Vitality (p=0.0005), Social Functioning (p=0.0369), Mental Health Index (p=0.0317), Standardized Physical Component (p=0.0002), and Standardized Mental Component (p=0.0338). The calculated NNT for OxyContin was 2.6. OxyContin was preferred by 88% (p=0.0001) of patients and in 80% of the cases by the investigator (p=0.0001). Ninety-five percent of patients completing the study rated OxyContin as moderately or highly effective.

Adverse events were similar between treatment groups. Nausea, constipation, dizziness, headache, vomiting, pruritus and sweating were more frequent in the OxyContin group than in the placebo group; however, of these adverse events, only incidence of constipation reached statistical significance (n=13, OxyContin vs. n=4, placebo; p=0.02). Four patients experienced serious adverse events during the study (n=1, OxyContin vs. n=3, placebo). The OxyContin patient suffered severe withdrawal symptoms during the washout period.

Patients who received benefit from the study were offered the opportunity to continue on open-label OxyContin treatment for up to one year. Thirty patients participated in the open-label OxyContin treatment, of whom 27 (90%) completed six months and 19 (63%) returned for their one year visit.

#### Studies in Patients with Pain associated with Post-herpetic Neuralgia

Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia**.**

*Neurology*. 1998;50(6):1837-1841.

Location: 1 center in Canada

Post-herpetic neuralgia (PHN) was used as a model to in a single-center, randomized, double-blind, placebo- controlled, two-way crossover study evaluating the efficacy and safety of OxyContin tablets compared to placebo in patients with neuropathic pain.

Patients with PHN (≥3 months) of at least moderate intensity for half a day were enrolled. Patients were excluded from the study if they were hypersensitive to opioids, intolerant to oxycodone, had a history of drug or alcohol abuse, or had significant pain of an alternative etiology.

Patients received OxyContin and placebo, each given for 4 weeks, with no intervening washout periods between treatments. The dose of OxyContin was increased weekly from 10 mg q12h up to a maximum of 30 mg q12h. Non-opioid analgesics (antidepressants, NSAIDs, or acetaminophen) that had been a part of the patient’s therapy for ≥3 weeks could have been continued during the study; however, other opioid analgesics were not allowed. Thirty percent of patients who had been taking antidepressants (usually amitriptyline) for the previous two months continued to take them at the same dose during the trial.

Primary measures of efficacy were overall pain intensity measured by daily visual analog scale (VAS) and categorical scores and weekly VAS and categorical scores for steady, brief, and skin pain intensity. Pain intensity was assessed by the patient in a daily diary, at the time of their evening dose of medication using the 100 mm unmarked VAS (bounded on the left by “no pain” and on the right by “unbearable pain”) and the five- point categorical pain intensity scale (CAT; 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain, 4=unbearable pain). The primary measure of disability was recorded weekly by the investigators (categorical disability scale: 0=no disability, 1=mild disability, 2=moderate disability, 3=severe disability).

Secondary measures of efficacy included pain relief, affective state, effectiveness of treatment, and patient preference. Pain relief was assessed using a 6-point categorical scale (0=pain worse, 1=no relief, 2=slight relief, 3=moderate relief, 4=a lot of relief, 5=complete relief). Affective state and effectiveness of treatment were assessed weekly by the patients (affective state was assessed using the Profile of Mood States Questionnaire [POMS] and the Beck Depression Inventory; effectiveness scale: 0=not effective, 2=slightly effective, 3=moderately effective, 4=highly effective), and patient preference was assessed after completion of each of the two crossover phases of the study. Pharmacokinetic and safety assessments were also performed.

Of the 50 patients enrolled, 38 patients (n=22, women vs. n=16, men; mean age, 70±11 years) completed both double-blind periods. In patients who completed the study, the time since onset of PHN was 31±29 months and daily duration of pain was 18±5 hours. The mean OxyContin dose during the first week was 21±7 mg/day and during the final week was 45±17 mg/day. As shown in **Table 16**, patients receiving OxyContin reported significantly lower mean daily pain intensity scores compared to placebo, except for pain VAS at the lowest dose during Week 1 (p=0.1234). Similarly, weekly pain intensity VAS scores and CAT scores were significantly lower with OxyContin than with placebo during the final week of treatment. OxyContin provided increases in weekly pain relief scores compared to placebo (2.9±1.2 vs. 1.8±1.1, respectively; p=0.0001). Compared with placebo, OxyContin showed significantly better scores for global effectiveness, disability, and patient preference (see **Table 16**).

The adverse event profile for OxyContin was typical of an oral opioid analgesic, and included constipation, nausea, and sedation. The number of patients reporting adverse events was greater with OxyContin than with placebo (76% vs. 49%, respectively; p=0.0074).

#### Table 16. Effect of 4 Weeks’ Treatment with OxyContin (q12h) vs. Placebo in Post-herpetic Neuralgia

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **OxyContin** | **Placebo** | **P-value** |
| **Primary** | | | |
| Daily Pain Intensity Score, mean (VAS, mm) | 35±25 | 54±25 | p=0.0001 |
| Daily Pain Intensity Score, mean (CAT) | 1.7±0.7 | 2.3±0.7 | p=0.0001 |
| Weekly Pain Intensity Score, mean (VAS, mm) – Steady Pain | 34±26 | 55±27 | p=0.0001 |
| Weekly Pain Intensity Score, mean (VAS, mm) – Brief Pain | 22+24 | 42±32 | p=0.0001 |
| Weekly Pain Intensity Score, mean (VAS, mm) – Skin Pain | 32±27 | 50±30 | p=0.0004 |
| Weekly Pain Intensity Score, mean (CAT) – Steady Pain | 1.6±0.9 | 2.3±0.8 | p=0.0001 |
| Weekly Pain Intensity Score, mean (CAT) – Brief Pain | 1.2±1.1 | 1.9±1.1 | p=0.0002 |
| Weekly Pain Intensity Score, mean (CAT) – Skin Pain | 1.6±1.0 | 2.0±1.1 | p=0.0155 |
| **Secondary** | | | |
| Daily Pain Relief | 2.9±0.1 | 1.9±1.0 | p=0.0001 |
| Clinical effectiveness\*(assessed by patients) | 1.8±1.1 | 0.7±1.0 | p=0.0001 |
| Disability† (rated by investigators) | 0.3±0.8 | 0.7±1.0 | p=0.041 |
| Patient preference (%)‡ | 67 | 11 | p=0.001 |

\*Effectiveness scale: 0=not effective; 1=slightly effective; 2=moderately effective; 3=highly effective.

†Disability scale: 0=no disability; 1=mild disability; 2=moderate disability; 3=severe disability.

‡Percentage of patients preferring this treatment phase; 22% of patients had no preference.

#### Studies in Patients with Postoperative Pain

Zhou B, Wang J, Yan Z, Shi P, Kan Z. Liver cancer: effects, safety, and cost-effectiveness of controlled- release oxycodone for pain control after TACE. *Radiology.* 2012 Mar;262(3):1014-21.

Location: 1 center in China; Study Dates: May 2009-Jul 2009

This prospective, randomized, double-blind, placebo-controlled study evaluated the analgesic effect, safety, and cost-effectiveness of controlled-release oxycodone (CRO) in regards to post-operative pain management following transarterial chemoembolization (TACE) in patients with liver cancer.

Patients with confirmed diagnosis of liver cancer, with no more than 3 tumors that were >3 cm and <8 cm in diameter were eligible to participate in the study. Exclusion criteria included: American Society of Anesthesiologist physical status >3; known allergy or intolerance to CRO; pregnancy; history of drug abuse; long-term opioid use; post-operative nausea, vomiting, or ileus; and liver dysfunction where enzyme elevation was greater than three times the reference range.

Patients were randomized to one of three groups: (1) 20 mg CRO 1 hour before TACE (T0) and 12 (T12) and 24 (T24) hours after T0; (2) 10 mg CRO, given at the same intervals as group 1; (3) placebo of 100 mg vitamin C, given at the same intervals as group 1. Both CRO and placebo were prepared in capsules with identical appearance. Incidents of acute pain post-TACE were managed with subcutaneous morphine 10 mg, followed by either 10 mg CRO or 20 mg or more of oral controlled-release morphine, if pain continued until the pain was controlled. Pain intensity was assessed using a 11-point numerical rating scale (NRS; 0-3=mild, 4- 6=moderate, 7-10=severe) every 4 hours, beginning 1 hour before TACE (T0) and continuing until 48 hours (T48) after T0. The highest pain score in specified time periods (T0-12, T12-24, and T24-48) was used for comparison amongst the three groups. Quality-of-life factors were rated by patients at T0 and T48 using a 5- point categorical scale (1=worst, 2=bad, 3=mild, 4=normal, 5=very good). Adverse events (AEs) were monitored and cost-effectiveness related to mean analgesic cost and hospital stay was assessed.

In total, 210 patients were randomized to one of the three groups (n=70 per group), and there was no significant difference in mean highest pain scores at T0 (p=0.71). The mean highest pain scores in groups 1 and 2 were significantly lower compared to group 3 for each time period (p<0.001). Additionally, the mean highest pain score in group 1 was significantly lower compared to group 2 during T0-12 (3.8±1.6 vs. 5.0±1.8; p<0.001), but was similar during T12-24 and T24-48 as shown in **Table 17**.

#### Table 17. Mean Highest Pain Scores

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment Period** | **Treatment Groups (n=70/group)** | | | **P-value\*** |
| **Group 1 (20 mg CRO)** | **Group 2 (10 mg CRO)** | **Group 3 (Placebo)** |
| T0 | 1.4±0.6 | 1.4±0.6 | 1.4±0.7 | 0.71 |
| T0-12† | 3.8±1.6 | 5.0±1.8 | 7.8±1.4 | <0.001 |
| T12-24 | 2.5±1.2 | 2.4±1.0 | 4.8±1.2 | <0.001 |
| T24-48 | 1.8±1.1 | 1.4±0.7 | 2.8±1.4 | <0.001 |

\*Compares difference in the highest pain scores during each time period among the three groups

†Group 1 vs. Group 2, p<0.001

Morphine consumption was lower in both groups 1 and 2 than in group 3, and lower in group 2 than in group 1 in all three treatment periods; however, p-values were not calculated.

Differences in quality-of-life scores between T0 and T48 suggest that recovery of quality of sleep, appetite, spirit, and fatigue were significantly better in groups 1 and 2 compared to group 3 (p<0.001). Appetite recovery was also significantly better in group 1 compared to group 2 (p=0.001). AEs included nausea, vomiting, dizziness, constipation, dysuria, hypersomnia, and pruritus, and no significant differences in AEs were observed among the three groups.

Regarding the cost-effectiveness analysis, analgesic cost and hospital stay in groups 1 and 2 was significantly less than in group 3 (median analgesic cost, Chinese Yuan: 37.0, group 1 vs. 19.6, group 2 vs. 43.4, group 3

[p=0.002]; mean hospital stay, days: 4.2±0.4, group 1 vs. 4.3±0.4, group 2 vs. 5.1±1.1, group 3 [p<0.001]). In a comparison of group 1 and group 2, cost was significantly lower in group 2 (p=0.001).

Rothwell MP, Pearson D, Hunter JD, et al. Oral oxycodone offers equivalent analgesia to intravenous patient- controlled analgesia after total hip replacement: a randomized, single-centre, non-blinded, non-inferiority study. *Br J Anaesth*. 2011;106(6):865-872.

Location: 1 center in the United Kingdom

A randomized, single-center, non-blinded, non-inferiority study was conducted to determine if OxyContin tablets are clinically equivalent to intravenous patient-controlled analgesia (IVPCA) with morphine in adult patients undergoing total hip replacement.

Patients, ages 60-85 years, with ASA health status class I-III who were undergoing total hip replacement and willing to undergo spinal anesthesia were eligible for participation in the study. Patients with the following characteristics were excluded from the study: weight <45 kg, long-term strong opioid therapy before operation, abnormal perioperative mental status, inability to operate an IVPCA device, or known allergy to oxycodone or morphine.

Following successful spinal block, patients (N=114) were randomized to one of two postoperative treatments: oral controlled-release oxycodone (OxyContin) 20 mg q12h for three days (n=57) and immediate-release oxycodone for breakthrough pain or IVPCA with morphine 1 mg bolus, 5 min lockout time, and no loading dose (n=57). Both groups received non-opioid co-analgesia and antiemetics.

Primary outcome measures were: (i) postoperative pain at rest and movement measured every 4 hours via numerical rating scale (NRS), 0-10, and (ii) nausea score recorded every 12 hours using a 0-4 scale (0=no nausea; 1=mild nausea; 2=antiemetic given; 3=nausea despite antiemetic; 4=vomiting). The secondary outcome measures included: (i) time to first mobilization, (ii) total amount of opioid consumed, (iii) number of additional antiemetic doses, and (iv) time to analgesic discontinuation.

Of the 114 patients randomized, two patients in each treatment group withdrew from the study due to intolerable nausea or vomiting. There were no statistically significant differences in the primary outcome measures of pain at rest and movement (p>0.05, 95% confidence intervals: -0.41, +0.96) or nausea scores (p>0.05) during any time period between the two treatment groups.

The secondary outcome measures showed no significant difference between OxyContin and IVPCA in regards to the mean total amount of opioid consumed (102 mg vs. 63 mg, respectively; p=0.053) and time to mobilization (24.45 h vs. 26.6 h, respectively; p=0.204). The number of antiemetic doses required in the first 24 hours was significantly lower in patients treated with OxyContin compared to IVPCA (1.1 vs. 1.4, respectively; p=0.03). Additionally, the time to analgesic discontinuation was significantly shorter in the OxyContin group (50.5 h, OxyContin vs. 56.6 h, IVPCA; p=0.042). There were no instances of significant respiratory depression in either group and no additional safety information was provided.

Kampe S, Wolter K, Warm M, Dagtekin O, Shaheen S, Landwehr S. Clinical equivalence of controlled-release oxycodone 20 mg and controlled-release tramadol 200 mg after surgery for breast cancer. *Pharmacology*.

2009;84(5):276-281.

Location: 1 center in Germany

A randomized, double-blind study evaluated the use of controlled-release oxycodone compared to controlled- release tramadol administered on a 12-hour dosing schedule for postoperative pain after surgery for breast cancer.

Patients, 18-80 years, schedule for surgery for breast cancer, who had ASA physical status I-III and weighed 40-100 kg were included in the study. Patients with known contraindications to oxycodone, tramadol, or paracetamol, communication difficulties, psychiatric disease, pregnancy, history of alcoholism, drug abuse, chronic pain, or sleep apnea syndrome were not eligible to participate in the study.

Female patients (N=54) were randomly allocated to 2 groups, receiving either 20 mg controlled-release oxycodone (n=27) or 200 mg controlled-release tramadol (n=27). All patients received premedication with 7.5 mg midazolam thirty minutes prior to surgery. A dose of either controlled-release oxycodone or controlled- release tramadol was given at time of premedication as well as 12 hours later. All patients had access to rescue medication post-surgery (1 gram IV paracetamol).

The primary variables for clinical equivalence were the differences between the mean values for pain scores at rest and on coughing 8-24 hours after operation. Pain scores were assessed using a 100-mm visual analog scale (VAS), ranging from 0 (no pain) to 100 (worst pain imaginable). Power calculations indicated that 27 patients in each treatment group would be adequate to prove equivalence with 95% power, 5% significance level, and an equivalence margin of ±10 on the VAS.

Of the 54 patients randomized to treatment, data from 1 patient, who required operative revision due to postoperative complications, was excluded. Mean pain scores at rest 24 hours post-surgery were similar between controlled-release oxycodone and controlled-release tramadol (5.4 [5.82] vs. 7.4 [8.59], respectively). The 90% CI of the mean differences between the treatment groups over 24 hours after operation at rest was found to be within the predefined equivalence margin (90% CI: -4.5 to +1.7). Controlled-release oxycodone and controlled-release tramadol were also found to be equivalent in regards to mean pain scores on coughing 24-hours post-surgery (6.2 [5.71] vs. 11.5 [21.43]; 90% CI: -6.2 to +1.7). Cumulative paracetamol given over the 24-hour observation period did not differ significantly between the oxycodone group and the tramadol group (1.32±1.9 g vs. 1.61±1.1 g; p=0.32).

There were no significant differences between the treatment groups regarding adverse events, such as nausea (p=0.13), vomiting (p=0.24), itching (p=0.77), sedation (p=0.97), and dizziness (p=0.35). Additionally, no significant differences were found concerning patient satisfaction scores (p=0.8) or patients' general perception of postoperative pain management (p=0.71).

Illgen RL, Pellino TA, Gordon DB, Butts S, Heiner JP. Prospective analysis of a novel long-acting oral opioid analgesic regimen for pain control after total hip and knee arthroplasty. *J Arthroplasty*. 2006;21(6):814-820.

Location: 1 center in US; Study Dates: Mar 2001-Oct 2003

A prospective study was conducted to compare the use of traditional intravenous patient-controlled analgesia (IVPCA) versus OxyContin in postoperative pain patients after total knee arthroplasty (TKA) or total hip arthroplasty (THA).

A preintervention and postintervention design was used where patients in the preintervention group received IVPCA either with morphine sulfate 1 to 2 mg or hydromorphone 0.2 to 0.4 mg with a 6-minute lockout for postoperative pain management between March 2001 and June 2003. Patients in the postintervention (new standardized postoperative orders) group received OxyContin 20 mg starting preoperatively the morning of surgery and continuing twice daily through postoperative day 3 (6 doses total) between July and October 2003. Patients were allowed a short-acting oral opioid (oxycodone 5 to 20 mg every 3 hours) as needed. Intravenous opioids were given only if the patient did not obtain satisfactory pain control or if they developed nausea or vomiting using the oral regimen.

Outcome measures included visual analog pain scores, total opioid consumption, functional interference measures, patient satisfaction, and rates of opioid-related side effects. Patients were surveyed each day at approximately the same time for three days about their experiences in the past 24 hours using a survey adapted from the American Pain Society’s Patient Outcome Questionnaire and the Brief Pain Inventory, and a medical record audit was completed for the same periods. Information was collected from patients’ charts regarding the total amount of opioid administered, side effect management, and physical therapy tolerance.

One hundred twenty-four patients were included in either a preintervention design group (n=62) or postintervention design group (n=62). No significant differences in any of the outcome measures tested were detected between THA and TKA groups; therefore, all data presented was the combined THA and TKA findings. Patients in both the OxyContin and IVPCA groups had similar pain ratings for all three days. Mean worst pain ratings were approximately 8 (range, 2-10) on postoperative day 1 and gradually decreased to a mean of 6 (range, 0-10) by day 3 in both groups. There was no difference in the amount of moderate to severe pain in either group. Patients in the OxyContin group used significantly less opioid (mean parenteral morphine equivalent) in the first 24 hours after surgery than patients using IVPCA (37.80 mg±23.45 vs. 59.41 mg±37.00, respectively, p<0.001). On days 2 and 3, IV opioid use was similar in both groups. Twenty-six (42%) patients in the OxyContin group received at least 1 parenteral rescue dose in the first 24 hours. By day 3, 80% of patients in the IVPCA group had been transitioned to oral opioids on as needed basis.

Patients in the OxyContin group reported significantly less interference from pain in walking (p=0.024) and coughing (p=0.022) on day 1, falling asleep (p=0.001), staying asleep (p=0.013), coughing (p=0.004), and deep breathing (p=0.011) on day 2, and getting out of bed (p=0.05), walking (p=0.038), staying asleep (p=0.001), coughing (p=0.003), and deep breathing (p=0.003) on day 3. No statistically significant differences were noted in length of stay for OxyContin compared to IVPCA. Patient satisfaction ratings reached a statistical difference by day 3 in favor of the OxyContin group versus the IVPCA group (p<0.05). No statistically significant differences in side effects were reported. On all 3 days, drowsiness was most frequently reported, followed by nausea, dizziness, and itching. By day 3, constipation became a frequently reported side effect.

de Beer J, Winemaker MJ, Donnelly GAE, et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. *Can J Surg*. 2005;48(4):277-283.

Location: Canada

Two separate (Phase I and Phase II), 3-week, open-label group studies evaluated pain intensity, pain relief, length of hospital stay, analgesic use, and side effects following administration of OxyContin and standard therapy (ST) for postoperative pain 48 hours after primary knee and hip replacement. Phase I examined treatment with OxyContin and Phase II examined treatment with standard analgesic therapy.

Patients scheduled to undergo elective primary unilateral total knee or hip replacement secondary to osteoarthritis and able to comply with the study protocol and complete study diaries were permitted to enter the study. Patients were excluded for the following reasons: allergy to an opioid, a history of drug abuse, ingestion of opioid analgesics within 24 hours before the operation, recipient of workers’ compensation benefits, inflammatory arthritis or significant pain of other origin.

For the first 48 hours postoperatively, patients received intravenous morphine through patient-controlled device (IVPCA) or epidural administration of a combination of morphine, fentanyl and bupivacaine. Upon discontinuation patients received only the following analgesics:

* + Phase I : OxyContin 10 mg, 20 mg, and 40 mg tablets; rescue medication consisted of morphine 7.5-10 mg intramuscularly (IM) every 3-4 hours as needed for severe pain (in hospital) and acetaminophen 325-650 mg orally every 4 hours as needed (after discharge), or
  + Phase II: Standard analgesics, according to physician’s written orders. The most common regimen was acetaminophen plus codeine (A/C 300 mg/30 mg) 1-2 tablets orally every 3-4 hours as needed. Rescue medication was meperidine IM every 3-4 hours as needed (in hospital) for severe pain and acetaminophen 325 mg as needed (after discharge). Alternative oral opioid analgesics included acetaminophen plus codeine (A/C 300 mg/15 mg) and oxycodone and acetaminophen combinations.

Phase I patients (n=70) received OxyContin 30 mg as their first dose of study medication on the morning of the second day after surgery (day 2). Baseline pain levels were recorded once pain was of moderate intensity, following discontinuation of IVPCA or epidural analgesia. Subsequent doses of OxyContin followed a structured dose de-escalation schedule. Patients who required rescue medication within the first 12 hour period on day 2 had their OxyContin dose increased up to 40 mg q12h. Then on days 4 and 5, these patients received 30 mg q12h; on days 6 and 7, they received 20 mg q12h; and on days 8-21, they received 10 or 20 mg q12h. Patients who did not require rescue medication within the first 12-hour period on day 2, remained on a dose of 30 mg q12h on days 2 and 3. Then they received 20 mg q12h on days 4, 5, and 6 and 10 or 20 mg q12h on days 7-21. Phase II patients (n=101) received ST after discontinuation of IVPCA or epidural analgesia, approximately 48 hour postoperatively. Baseline pain was recorded concomitant with the cessation of IVPCA or epidural administration. ST was based on physician’s written orders.

Efficacy and safety evaluations were based on the patient diary and on assessments completed by patients during the first 4 hours after the first dose of study medication and during the follow-up visit. Pain intensity was assessed using a 100-mm visual analog scale (VAS). The VAS was an unmarked line, bounded on the left by “no pain” and on the right by “excruciating pain.” During the hospital stay, patients were issued a daily diary (diary 1) to complete the visual analogue and categorical scales for pain intensity and pain relief 3 times per day (morning, afternoon, and evening). In both Phase I and Phase II, the times to first rescue analgesic, the dose of rescue analgesics and the number of rescue analgesics used by each patient were also recorded, with the addition of time and type of analgesic taken recorded in Phase II.

For an additional 2 weeks after discharge, patients in Phase I recorded in the daily diary (diary 2) the number of OxyContin tablets they took and the date and time they were taken. Also patients were instructed to document the date, time and the number of acetaminophen 325 mg tablets taken to alleviate pain that was not

controlled following the appropriate dose of OxyContin. Diary 2 contained the same visual analogue and categorical scale assessments as those in diary 1. In Phase II, patients recorded the same measures as Phase I for all analgesics taken.

In both phases, at 2 weeks postoperatively, patients were asked to complete Brief Pain Inventory (BPI) short form, where most questions were scored on a 0-10 scale (0=no pain or difficulty, 10=maximum pain or difficulty). A composite pain score (Pain Intensity) and composite functional ability score (Functional Impairment) were calculated by summing the appropriate individual items for each. In addition, a pain relief measure (% of relief afforded) and hours measure (the number of hours for which pain medications were not required) was reported.

At the time of discharge from the hospital, patients in the OxyContin group recorded lower mean [standard deviation] VAS pain intensity scores than the ST group (20.2 [17.9] vs. 27.7 [21.5]; p=0.021). Length of hospital stay was 5.5 and 6.4 days for the OxyContin and ST groups, respectively (p<0.001). OxyContin patients used significantly less opioid (morphine equivalents) while in hospital than ST patients (p<0.001), and the average number of daily administrations of analgesics in hospital was significantly less for OxyContin and ST patients (2.1 vs. 3.5, respectively; p<0.001).

Summary of the BPI at 2 weeks postoperatively found pain equally well controlled between phases, although patients displayed less functional impairment in Phase I (see **Table 18** below). Standard therapy patients reported more nausea and vomiting, pruritus, and fever than the OxyContin patients, but less somnolence, constipation, dizziness, confusion, and tachycardia.

#### Table 18. Summary of the Brief Pain Inventory Scores 2 Weeks Postoperatively

**tandard Therapy (Phase II)**

|  |  |  |
| --- | --- | --- |
| **Category** | **Mean (SD) Total** | **Score** |
| **OxyContin S**  **(Phase I)** | |  |
| Pain Intensity | 11.3 (6.8) | 12.7 (6.6) |
| Functional Impairment | 22.9 (13.7) | 29.2 (16.2)\* |
| Pain relief, % | 75.9 (19.1) | 73.4 (24.3) |
| Hours between medication doses | 5.6 (1.2) | 5.1 (1.2)† |

\*p=0.014, †p=0.013

Wirz S, Wartenberg H, Wittmann M, Nadstawek J. Post-operative pain therapy with controlled-release oxycodone or controlled release tramadol following orthopedic surgery: A prospective, randomized, double- blind investigation. *The Pain Clinic*. 2005;17(4):367-376.

A prospective, randomized, double-blind study compared the efficacy and safety of controlled-release (CR) oxycodone and CR tramadol for the management of post-operative pain.

Patients (ages, 18-65 years) with ASA classification I-II, scheduled for orthopedic surgery of the lower extremities were enrolled in this study. Exclusion criteria included the following: known or suspected cardiovascular, pulmonary, renal, neurological, psychiatric or allergic diseases; lactation or pregnancy; drug dependency; alcoholism; opioid tolerance; history of abuse or history of treatment with any opioids; and current treatment with analgesics other than the study medications.

Patients underwent a standardized general anesthesia. Based on recognized conversion factors to morphine, a conversion factor of 10/1 for oral tramadol and oxycodone was calculated. Post-operative administration of study medications was fixed at 6AM and 6PM. A single-dose of either 100 mg tramadol or 10 mg oxycodone immediate-release was permitted for treating acute exacerbation of pain. If pain control was still insufficient, NSAIDs were allowed. Dosage, pain symptoms, and vital signs were recorded at 7AM, 2PM, 7PM, and 10PM over three days post-surgery. Numerical rating scales (NRS; 0=no pain, 100=worst pain imaginable) were used to assess pain at rest and while exercising. Adverse events (AEs), including nausea, vomiting, sedation, dizziness, dry mouth, or pruritus, were also assessed via NRS. Occurrences of sleep disturbances (sleep onset and sleep maintenance-insomnia), nightmares, and myoclonus were also noted on a two-step scale (no- yes).

Eligible patients (N=57) were randomized to either CR oxycodone (n=26) or CR tramadol (n=31). Mean daily doses for CR oxycodone and CR tramadol were 21.03 mg and 211.83 mg, respectively. Pain at rest and during exercise over days 1-3 were not significantly different between the two treatment groups. When comparing pain levels on day 1 vs. day 3, both treatments were associated with significant decreases in pain at rest as noted for all four time points. Pain during exercise did not significantly differ on day 1 vs. day 3 with either treatment. Additionally, there was no significant difference in the need for rescue analgesia in either treatment group.

No AEs were deemed severe by investigators. In regards to the symptom assessment, nausea was significantly more severe with CR tramadol compared to CR oxycodone (NRS: 6, CR oxycodone vs. 15, CR tramadol; p=0.011). Emesis and nightmares occured only with CR tramadol (n=15, n=4; respectively).

Additionally, myoclonus, sleep onset insomnia as well as sedation were more severe or frequent with CR tramadol, while dryness of mouth was reported as more severe with CR oxycodone; though not significantly.

Kampe S, Warm M, Kaufmann J, et al. Clinical efficacy of controlled-release oxycodone 20mg administered on a 12-h dosing schedule on the management of postoperative pain after breast surgery for cancer. *Curr Med Res Opin*. 2004;20(2): 199-202.

Location: Germany

A prospective, randomized, placebo-controlled, double-blind study involving women undergoing breast surgery for cancer was conducted to compare the use of either OxyContin 20 mg or placebo 1-hour prior to surgery and again 12-hours after the first dose for the management of postoperative pain.

All subjects were pre-medicated with oral midazolam 7.5 mg, one hour before surgery. General anesthesia using propofol and remifentanil was administered for surgery. Upon transfer to the recovery room, both groups had access to intravenous patient controlled analgesia (IVPCA) with piritramide (an opioid used commonly in Europe) for management of postoperative pain. Postoperative assessments were performed at 0, 4, 8, 16, and 24-hours after arrival in the recovery area. The primary efficacy endpoint was area under the curve (AUC) based on IVPCA opioid consumption over 24 hours postoperatively. Patients were instructed to record their wound pain at rest and on movement using a 100-mm visual analog scale (VAS), and the quality of pain management was assessed by the patients using a 4-point scale (1=poor; 4=excellent). The AUCs for these measurements served as secondary efficacy endpoints. Blood pressure, heart rate, and respiratory rate were monitored at each assessment and adverse events were documented.

Of the 40 patients eligible to participate, half were randomized to either treatment (OxyContin, n=20; placebo, n=20). The primary efficacy endpoint, AUC based on IVPCA opioid consumption over 24 hours postoperatively, was significantly lower for OxyContin compared to placebo (146±100 mg x time vs. 252±147 mg x time, respectively; p=0.01). The AUC for VAS scores at rest was significantly lower for OxyContin compared to placebo (92±91 mm x time vs. 188±193 mm x time, respectively; p=0.05). However, there was no significant difference in AUC for VAS scores on movement between OxyContin and placebo (324±323 mm x time vs. 504±359 mm x time, respectively; p=0.103), and there was no significant difference in overall quality of analgesia between OxyContin and placebo (89±9 score x time vs. 83±17 score x time, respectively; p=0.139).

No patient withdrew from taking study medication or dropped out. Fourteen adverse events were recorded in the OxyContin group and 11 adverse events were recorded in the placebo group. The most common adverse event with both OxyContin and placebo was nausea (55% and 35%, respectively; p=0.34). No patients demonstrated signs of confusion, agitation, respiratory depression, pruritus, arterial hypotension, hypertension, bradycardia, or tachycardia.

Ginsberg B, Sinatra RS, Adler LJ, et al. Conversion to oral controlled-release oxycodone from intravenous opioid analgesic in the postoperative setting. *Pain Med*. 2003;4(1):31-38.

Location: 7 Centers in US; Study Dates: Oct 1996-Jun 1997

In this multicenter, open-label, usual-use study of hospitalized patients that had undergone a variety of elective surgical procedures and received intravenous (IV) opioid therapy in the immediate postoperative period, patients were converted at least 12 hours after surgery to OxyContin for up to seven days in order to assess the effectiveness and safety of conversion factors used by investigators.

The study included hospitalized patients (ages, 18-70 years) recovering from elective major surgery (abdominal, orthopedic, gynecologic, or urologic) who had been treated postoperatively with IV opioid analgesics for at least 12 hours after surgery, either by continuous infusion or IV patient-controlled analgesia (IVPCA). Patients who were anticipated to require opioid analgesia for more than a few days were enrolled when they could tolerate oral medications. Patients with evidence of paralytic ileus, nausea and vomiting, significant respiratory depression, or other known contraindications to opioid therapy were excluded.

The initial OxyContin dose was determined by the treating physician based on the IV opioid dose during the previous 12-24 hours and the current pain intensity of the patient (IV morphine 24 hour requirement multiplied by a conservative conversion factor of 1.5 equals the oral oxycodone dose mg/day). Patients were treated with OxyContin q12h for a maximum of seven days, throughout which the OxyContin dose was titrated upward or downward based on clinical response. Upward dose adjustments of the initial OxyContin dose were allowed if the patient had been poorly controlled by the IV opioid dose and downward adjustments were permitted if pain was expected to improve rapidly or if the patient had been experiencing dose-limiting side effects with the IV opioid (dose titration of ±25-50%). The recommended supplemental analgesic was immediate-release (IR) oxycodone administered every 4-6 hours as needed at a dose of 1/4 to 1/3 of the q12h OxyContin dose.

NSAIDs were allowed if considered appropriate. Since this was a usual-use study, other concomitant medications (except for opioids) could also be prescribed.

Patients were asked to rate pain intensity using an 11-point numerical rating scale (NRS; 0=no pain, 10=worst possible pain), where scores 4 were considered indicative of adequate pain control. The comfort level scale (0=poor, 10=very comfortable) as well as the quality of sleep and patient acceptance scales (0=poor, 10=excellent) were used. The primary endpoints evaluated included average daily dose of OxyContin, postoperative day of conversion to OxyContin, average conversion factors, average daily dose of supplemental IR oxycodone, and pain intensity scores. Secondary endpoints included average comfort level scores, quality of sleep, and acceptance of therapy. Adverse events (AEs) were also monitored.

In total, 189 patients (mean age, 44 years; age range, 20-69 years) were converted to OxyContin and evaluated for effectiveness and safety, and 139 patients (74%) completed the study by remaining on OxyContin until opioid therapy was no longer required or for a maximum of 7 days. The majority of patients were converted to OxyContin on the first postoperative day (59-67% of those patients undergoing abdominal, orthopedic, and gynecologic surgery). For all patients, the initial OxyContin dose averaged 29 (±2 SE) mg q12h, with the highest dose being used in patients recovering from orthopedic surgery.

At 6 hours after the initial OxyContin dose, patients reported significantly lower pain intensities than with IVPCA for all patients combined (mean NRS pain scores: 4.1±0.2, baseline vs. 3.3±0.2, 6 hours post initial OxyContin dose; p=0.0003). Patients remained on OxyContin therapy for a mean of 4.3±0.2 days. One-third of patients required around-the-clock OxyContin therapy for at least 7 days, with the mean daily doses declining from 56±3 mg on the 1st day to 27 mg±3 mg on the 7th day.

Mean current pain intensity scores at baseline and at 6 hours after the initial OxyContin dose, respectively, grouped by conversion factor were: 1.0 (4.2, 3.6); >1.0 to 1.5 (4.4, 3.5); and >1.5 (2.9, 2.1). Mean conversion factors for patients converting from IV morphine to OxyContin for the various types of surgery ranged from 1.2 to 1.3. The mean conversion factor from IVPCA morphine to OxyContin in this study of

1.2±0.1 SE was determined to have provided effective analgesia, especially in an acute postsurgical model where pain intensity is expected to decrease on a daily basis.

Regarding secondary endpoints, during the first 48 hours following conversion to OxyContin, fewer rescue doses were taken when higher conversion factors were utilized. The number of patients requiring rescue medication also decreased over time, from 62% of patients on day 1 to 38% on day 7. Overall, patients used an average of one IR oxycodone dose of rescue medication per day. Patients reported an adequate level of comfort with mean scores >7 at 6 hours after the morning dose of OxyContin and throughout the study, and the acceptance of medication score at the end of the study was 8.2±0.7. Quality of sleep improved from a baseline score of 5.0±0.2 to 6.8±0.2 on day 2 to 7.8±0.3 on day 7.

The most commonly reported AEs were constipation, nausea, and pruritus, occurring in 10% of patients and were also the most common AEs leading to dose reduction of OxyContin (n=29) or premature discontinuation (n=29). The most clinically significant AEs reported during the study were constipation and paralytic ileus.

Cheville A, Chen A, Oster G, et al. A randomized trial of controlled-release oxycodone during inpatient rehabilitation following unilateral total knee arthroplasty. *J Bone Joint Surg*. 2001;83-A(4):572-576.

Location: 2 rehabilitation centers in New Jersey

A randomized, double-blind, placebo-controlled study conducted at two affiliated, freestanding, acute rehabilitation facilities evaluated the effectiveness of OxyContin compared with usual care with as needed (PRN) immediate-release (IR) oxycodone in the control of postoperative pain, functional recovery, and time in rehabilitation.

Patients who had been transferred to a rehabilitation hospital within seven days following elective, unilateral total knee arthroplasty were screened for inclusion in the study. Patients who spoke English, had moderate to very severe pain, could bear weight fully in the involved extremity, had no history of substance abuse, and had no evidence of cognitive impairment were eligible for inclusion in the study.

Eligible patients were randomized to OxyContin every 12 hours (20 mg qAM, and 10 mg qPM) or placebo. Both groups were also able to receive IR oxycodone (5 mg q4h, PRN) as rescue medication. The OxyContin dose was titrated upward for patients who received three or more rescue doses of IR oxycodone on two consecutive days. Upward titrations in increments of 10 mg were continued up to a maximum daily dose of OxyContin of 60 mg. All patients participated in a standard, rigorous physical therapy program for 3 hours each day.

Sociodemographic characteristics, visual analog scale (VAS) pain scores before and after surgery, degree of arthritis in other joints, and duration of pain in the operative knee were recorded at baseline. VAS pain scores were recorded immediately following each full, weekday physical therapy (PT) session. Subjects were asked to rate their pain “right now” and “at worst during PT,” and the degree to which pain affected their ability to participate in PT. Initial and final assessments of physical performance were made at PT sessions one and eight by the physical therapist. Active and passive knee range of motion (ROM), knee extensor torque, safe ambulation velocity, and Functional Independence Measure (FIM) scores (walking ability, sit-to-stand transfers, and stair climbing) were collected to assess patient functional status. The Memorial Symptom Assessment Scale (MSAS) was administered following the sixth physical therapy session to assess the presence and severity of any opioid-related side effects. Length of hospital stay and plans for any additional physical therapy were recorded at the time of discharge.

A total of 135 patients were screened, and 59 patients were randomized to either treatment. Baseline demographic, clinical, and functional characteristics were similar between the OxyContin and placebo groups. Patients who received OxyContin reported significantly less pain and greater knee ROM (passive, p=0.036; active, p<0.001) and extensor strength (p=0.001) by the eighth PT session compared to the placebo group.

OxyContin patients were discharged from the hospital an average of 2.3 days earlier than the patients in the placebo group (p=0.013). Overall, patients in the OxyContin group experienced enhanced pain control, reduced anxiety, accelerated functional recovery, and reduced need for inpatient rehabilitative services.

OxyContin patients requested an average of 1.9 doses/day of rescue medication compared to 2.6 doses/day among those in the placebo group (p=0.02). The total daily consumption of oxycodone was four times higher in the OxyContin group than in the placebo group (54.4 mg vs. 12.9 mg, respectively; p<0.001); however, the comparison of MSAS scores revealed no difference between the two groups in opioid-related side effects (p=0.83).

#### Long-term Studies in Patients with Noncancer Pain

Richarz U, Waechter S, Sabatowski R, Szczepanski L, Binsfeld H. Sustained safety and efficacy of once-daily hydromorphone extended-release (OROS® hydromorphone ER) compared with twice-daily oxycodone controlled-release over 52 weeks in patients with moderate to severe chronic noncancer pain. *Pain Pract*.

2013;13(1):30-40.

Binsfeld H, Szczepanski L, Waechter S, Richarz U, Sabatowski R. A randomized study to demonstrate noninferiority of once-daily OROS hydromorphone with twice-daily sustained release oxycodone for moderate to severe chronic noncancer pain. *Pain Pract*. 2010;10:404-415.

Location: 64 international centers, 20 of which participated in extension

An international, multicenter, open-label, randomized, parallel group, 24-week study with an optional 28-week extension phase (weeks 24 through 52) evaluated non-inferiority of twice-daily, controlled-release oxycodone (CRO) vs. once-daily, extended-release hydromorphone (ERH) in patients with chronic, non-cancer pain.

Patients aged ≥18 years with chronic, non-cancer pain, defined as pain occurring ≥20 days/month for >3 months, who required continuous opioid therapy were eligible to participate.

Initial doses were either 8 mg ERH once daily or 10 mg CRO twice daily, followed by titration over 4 weeks to a maximum daily dose of 32 mg or 80 mg, respectively. Patients continued treatment from week 0 through week 52, and the follow-up period consisted of weeks 53 to 56. Supplemental analgesia with acetaminophen (up to 2 grams/day) was permitted, as was bisacodyl to prevent constipation. The primary efficacy measures were the change in score on the 11-point Brief Pain Inventory (BPI) “pain right now” item from baseline to week 24 (core phase), where a non-inferiority margin of 1 point was considered a clinically significant difference, and then baseline to week 38 and week 52 (extension phase).

Secondary efficacy measures included the BPI “pain at its worst” and “pain relief” items, as well as pain- interference items. The BPI sleep interference item and the Medical Outcomes Study sleep item were used to assess sleep at weeks 24, 38, and 52. Quality of life at these visits was assessed with the Short-Form 36.

Global assessment of efficacy and assessment of convenience of the study drug occurred at week 52. Adverse events (AEs) were monitored from the first through the last dose of medication, and a global assessment of tolerability was performed at week 52.

Of the 277 patients who completed the 24-week core phase of the study, 112 patients (n=60, ERH; n=52, CRO) enrolled in the 28-week open-label extension phase of the study. Fifteen patients (13.4%) discontinued therapy during the extension phase; five due to AEs.

Patients who did not enter the extension phase had a mean exposure to ERH of 110.8 days and 112.9 days for CRO. The mean duration of exposure to ERH was 371.0 days compared to 380.5 days of CRO treatment. The mean ERH dose increased from 16.1 mg/day at week 4 (end of titration phase) to 17.1 mg/day at week 52 (end of extension phase). The mean CRO dose increased from 40.4 mg/day at week 4 (end of titration phase) to 44.6 mg/day at week 52 (end of extension phase).

There was a similar decrease in “pain right now” scores from baseline to the end of the core phase for both treatment groups. The difference in the means was 0.29, indicating that the two treatments were non-inferior to one another.5 Mean (SEM) change in “pain right now” from baseline to week 38 was -3.0 (0.3) for ERH compared to -2.8 (0.3) for CRO, changing little by week 52 (-2.9 [0.3] vs. -2.8 [0.3], respectively) as shown in

#### Table 19.

#### Table 19. Primary Efficacy Measure Results

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment** |  | **“Pain right now” Scores** |  |  |
|  | **Baseline** | **Week 52** | **Mean Change** |  |
| ERH | 6.8 (0.2) | 3.9 (0.3) | -2.9 (0.3) |  |
| CRO | 6.9 (0.2) | 4.1 (0.3) | -2.8 (0.3) |  |

Mean “pain at its worst”, “pain at its least”, pain interference scores, and SF-36 scores improved from baseline to week 52 with both treatments as described in **Table 20**.

#### Table 20. Secondary Efficacy Measure Results

|  |  |  |
| --- | --- | --- |
| **Secondary Efficacy Measures** | **ERH** | **CRO** |
| **Mean (SEM) Pain at its Worst Scores** | | |
| Baseline | 8.1 (0.2) | 8.1 (0.2) |
| Week 52 | 5.3 (0.3) | 5.7 (0.3) |
| **Mean (SEM) Pain at its Least Scores** | | |
| Baseline | 4.5 (0.2) | 4.8 (0.3) |
| Week 52 | 2.6 (0.2) | 2.4 (0.2) |
| **Mean (SEM) Pain Interference Scores** | | |
| Baseline | 6.6 (0.2) | 7.0 (0.3) |
| Week 24 | 4.2 (0.3) | 4.3 (0.2) |
| Week 38 | 3.9 (0.3) | 4.7 (0.3) |
| Week 52 | 4.2 (0.3) | 4.4 (0.3) |
| **Mean (SEM) SF-36 Pain Scores** | | |
| Baseline | 20.6 (1.6) | 16.4 (1.6) |
| Week 52 | 46.0 (3.6) | 41.9 (2.9) |

Sleep quality improved in both treatment groups from baseline to week 38 and to week 52 (mean change [SEM] through week 38: -12.5 [2.7], ERH vs. -12.4 [3.0], CRO; mean change [SEM] through week 52: -10.7

[2.4], ERH vs. -11.5 [2.7], CRO).

Patient-rated global assessments were similar between treatment groups, with 91.7% of ERH patients and 86.5% of CRO patients rating efficacy as “very good/good.” More patients in the ERH group rated their therapy as “very convenient” compared to patients treated with CRO (35% vs. 21.2%, respectively).

During the core phase (through week 24), 81% (n=206) of ERH patients and 85% (n=212) of CRO patients experienced at least one AE. Majority of the total AEs (90%) were deemed to be mild or moderate in severity. Body systems that were most affected were the gastrointestinal system (nausea, vomiting, diarrhea, and constipation), the nervous system (headache, dizziness, and somnolence), and the skin (hyperhidrosis and pruritus). Seventy-one serious AEs, most commonly related to the gastrointestinal tract, were reported by 46 (9%) patients; 9 patients in each treatment group withdrew from the study due to a serious AE. Of the 71 serious AEs, 8 in each treatment group were classified as related to study medication.

In the extension phase, AEs were reported by 85 patients (n=42, ERH; n=43, CRO). The most common AEs (>5% of patients) associated with ERH included weight decrease (6.0%), anorexia (6.0%), and hypertension (6.0%); those with CRO included nasopharyngitis (6.4%), vertigo (6.4%), and drug withdrawal syndrome (6.4%). The majority of the AEs occurring with both treatments were regarded as mild to moderate in severity. Serious AEs, most commonly either gastrointestinal disorders or surgical and medical procedures, occurred in six patients (12%) receiving ERH compared to four patients (8.5%) receiving CRO. No deaths during the study were reported. At week 52, tolerability of both ERH and CRO was rated as “very good/good” in 88.3% and 88.5% of patients, respectively.

Gatti A, Longo G, Sabato E, Sabato AF. Long-term controlled-release oxycodone and pregabalin in the treatment of noncancer pain: an observational study. *Eur Neurol*. 2011;65(6):317-322.

Location: 1 center in Italy; Study Dates: Jul 2008-Jan 2010

A 1-year, single-center, open-label, prospective cohort study evaluated the efficacy and tolerability of the long- term use of combination therapy with OxyContin and pregabalin in patients with chronic non-cancer pain who had not responded to other analgesic regimens.

All adult patients (age, ≥18 years) requiring medical attention at the facility who were experiencing chronic non- cancer pain, defined as a score of >5 on an 11-point numerical rating scale (NRS; 0 = “no pain,” 10 = “worst pain imaginable”) for ≥6 months, were offered participation in this study during the 18-month enrollment period.

Patients received OxyContin and pregabalin for a total period of one year, administered according to approved product information. Initial doses were determined from international guidelines, based on the patient’s condition and severity of pain. Oral morphine (5 or 10 mg/day) was provided for management of breakthrough pain.

Pain intensity over the last 24 hours was rated by patients at scheduled study visits (months 1, 2, 4, 6, 9, and

12) using an 11-point NRS, and dosage adjustments were permitted based on patient’s pain intensity rating. Adverse events (AEs) were recorded at each follow-up visit. Patients skipping a scheduled visit were considered lost to follow up, but an attempt was made to contact them by telephone at one week from study withdrawal and one month following the first interview to assess for onset of addiction; prescription records were checked for this purpose, as well.

A total of 1,015 patients (640 females) with a mean age of 64±15 years (range, 21 - 94 years) were enrolled in this study. The mean OxyContin starting dose was 12.5±8.4 mg/day (range, 10 - 100 mg/day), and the mean pregabalin starting dose was 121.7±97.2 mg/day (range, 50-600 mg/day). During the first four months, the mean OxyContin dose increased. After month 4, the mean OxyContin dose decreased (some of the significant increase at month 4 was driven by subjects who eventually discontinued participation due to AEs.) The mean OxyContin dose at month 12 was the lowest at any time. A similar trend (mean dose increased up to month 6, then decreased at months 9 and 12) was seen for pregabalin, but the 12-month mean daily dose was higher than the mean dose at baseline and months 1 and 2.

Throughout the 1-year study period, mean NRS scores significantly decreased (7.02±1.26 at baseline vs. 1.45±0.92 at 12 months, p=0.00001), and significant improvements were observed between consecutive visits (p<0.001).

A total of 234 patients (23% of enrollees) discontinued participation during the study due to AEs (n=159), complete relief from chronic pain (n=46), and lost to follow up (n=29). Most AEs reported were deemed mild to moderate in severity. The greatest number of withdrawals due to AEs occurred in month 1. The AEs cited most frequently as the reason for study withdrawal included constipation (22%), somnolence (15.1%), and nausea (13.8%). The reports of nausea and somnolence decreased significantly between all consecutive visits (p<0.05), but reports of constipation did not change significantly over time (**Table 21**). Three patients (all >65 years of age) with serious, pre-existing diseases died during the study (n=1, brain ischemia; n=2, heart failure). No cases of addiction were reportedly identified.

#### Table 21. Adverse Events During One Year of OxyContin and Pregabalin Treatment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Adverse Event** | **Number of Patients Reporting Selected Adverse Events At Scheduled Visit** | | | | | |
| **1 month** | **2 months** | **4 months** | **6 months** | **9 months** | **12 months** |
| Nausea | 243 | 213 | 165 | 101 | 79 | 25 |
| Constipation | 295 | 311 | 279 | 254 | 223 | 211 |
| Somnolence | 211 | 199 | 176 | 112 | 93 | 67 |
| Edema | 144 | 101 | 25 | 0 | 0 | 0 |

p<0.05 for all comparisons between consecutive visits (except for constipation [whole study] and edema (last three visits)

Giuggioli D, Manfredi A, Colaci M, Ferri C. Oxycodone in the long-term treatment of chronic pain related to scleroderma skin ulcers. *Pain Med*. 2010;11(10):1500-1503.

Location: 1 center, Italy

A single-center, open-label study was conducted to evaluate the efficacy and safety of long-term treatment with OxyContin for the management of severe chronic pain related to scleroderma skin ulcers.

Patients included in the study met the American College of Rheumatology classification criteria for Systemic Sclerosis and experienced severe pain (categorized per World Health Organization guidelines) due to skin ulcers uncontrolled by maximum doses of both NSAIDs and tramadol.

Patients were initiated on OxyContin 10 mg every 12 hours with dosage adjustments made to obtain complete pain relief. All patients continued systemic (calcium-channel blockers and/or prostanoids) and local (surgical debridement and moist dressing) standard therapies for the management of scleroderma skin ulcers. Patients participated in self-evaluation of their (1) pain using a visual analog scale (VAS) every evening, (2) use of other analgesics, (3) number of hours of sleep per night, and (4) side effects. Pittsburgh Sleep Quality Index (PSQI) questionnaire was completed at baseline, after 1 month, and at the end of treatment while the Health Assessment Questionnaire-Disability Index (HAQ-DI) was administered at baseline and at the end of treatment. In addition to monitoring of patient-reported side effects, vital signs and laboratory parameters were monitored at each monthly visit.

Of the twenty-nine patients (mean age, 52.3±12.9 years) included in the study, all experienced a significant reduction in skin ulcer-related pain after treatment with OxyContin (mean dose range, 20-40 mg/day), administered for a duration of 7.9±3.2 months. After one month of OxyContin treatment, VAS pain scores significantly decreased from 93.8±8.72 to 56.7±10.4 (p<0.0001); VAS pain scores further improved to 42.9±14.9 after three months of therapy and remained stable through the remainder of the study. Total number of hours of sleep also significantly improved after 1 month of therapy (3.68±1.28 hours, baseline vs. 5.27±0.75 hours, month 1; p<0.0001) and continued to improve through month 3 (6.10±0.95 hours). Additionally, PSQI significantly decreased from 9.72±3.95 to 3.37±1.04 after 1 month of OxyContin therapy (p<0.0001) and remained stable through month 3 of treatment, suggesting a better quality of sleep. HAQ-DI scores also decreased from 1.1±0.67 at baseline to 0.46±0.46 at the patients’ last evaluation. The number of patients requiring additional analgesia (NSAIDs, morphine, paracetamol plus codeine) decreased from 11 patients after 1 month of the therapy to 8 patients after 3 month of therapy.

No severe adverse events related to OxyContin treatment as well as changes in physical examination or laboratory parameters were observed during the entire study. Fifteen patients (51.7%) reported constipation after 1 month of OxyContin treatment, which was controlled with fiber supplementation and/or laxatives. An additional 9 patients (31%) reported itch, nausea, and/or dizziness. No patient reportedly presented with abstinence phenomenon after discontinuation of OxyContin.

Wild EJ, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Practice*. 2010;10(5):416-427.

Location: 53 centers in North America and 36 centers in Europe

A 1-year, open-label, phase 3, randomized, multicenter, parallel group, active-controlled, study with the primary objective of assessing the long-term safety profile and tolerability of extended-release tapentadol (TER) for the management of chronic low back pain or osteoarthritis (OA) of the knee or hip was conducted.

Adults (age, ≥18 years) with a diagnosis of moderate to severe knee or hip OA pain or low back pain of nonmalignant origin, with at least a 3-month history of pain prior to screening and who were dissatisfied with their current analgesic therapy were eligible to participate. Patients were required to have a pain intensity score of at least 4 on an 11-point numerical rating score (NRS) at baseline following a 3- to 7-day washout of all prior analgesic treatments.

Patients were randomized (4:1 ratio) to receive TER twice daily (100 mg to 250 mg) or OxyContin twice daily (20 mg to 50 mg) for up to one year. Efficacy was assessed at each visit on the NRS of average pain intensity over the previous 24 hours. Adverse events (AEs) were recorded through the follow-up period. Patients recorded severity of constipation symptoms on the Patient’s Assessment of Constipation Symptoms (PAC- SYM) questionnaire (5-point scale; 0=absence of symptoms to 4=very severe symptoms) at baseline, twice during the treatment period, and at the end of the study. Opioid withdrawal syndrome following discontinuation of treatment was measured utilizing the Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opiate Withdrawal Scale (SOWS). The categorical ranges on the COWS are: <5=no withdrawal; 5-12=mild withdrawal; 13-24=moderate withdrawal; 25-36=moderately severe withdrawal; and >36=severe withdrawal; with 48=maximum possible score. SOWS scores can range from 0 to 60, where 60 indicates extremely severe withdrawal.

A total of 1,117 patients (n=894, TER; n=223, OxyContin) were randomized and received at least one dose of study drug (the safety population), and 1,095 patients comprised the intent-to-treat (ITT) population (n=876, TER; n=219, OxyContin). Four-hundred thirteen patients in the TER group completed the study (46.2%) and 78 patients completed in the OxyContin group (35%). Study medication was taken for at least 6 months by 54.5% (n=487) of patients in the TER group and 41.1% (n=92) of patients in the OxyContin group, and for at least one year by 25.4% (n=227) of the TER group and 19.6% (n=44) the OxyContin group.

Among patients who completed the study, mean pain intensity scores decreased rapidly in both groups during the first 4 weeks of the study and then remained relatively stable. For patients who completed the study, the mean (SD) total daily dose for TER was 380.5 mg (102.43) and 71 mg (22.89) for OxyContin. In the TER group, mean (SE) pain intensity scores decreased from 7.6 (0.05) at baseline to 4.4 (0.09). In the OxyContin group, the decrease was from 7.6 (0.11) to 4.5 (0.17).

Overall, 85.7% (n=766) of the TER group and 90.6% (n=202) of the OxyContin group experienced at least one treatment-emergent adverse event (TEAE). The most common TEAEs (reported by >10% in either treatment group) included constipation, nausea, dizziness, somnolence, headache, fatigue, vomiting, and pruritus, as shown in **Table 22**. The distribution of time to first onset of TEAEs of nausea, vomiting, or constipation were significantly different between TER and OxyContin (p<0.001). The reporting rate of first TEAE of nausea, vomiting, or constipation increased in the first four weeks and then stabilized. TEAEs were the most common reason for treatment discontinuation in both groups (22.1%, TER; 36.8%, OxyContin). The incidence of serious TEAEs was 5.5% (n=49) in the TER group and 4% (n=9) in the OxyContin group. There were no deaths during the study.

#### Table 22. Treatment-emergent Adverse Events Reported by > 10% of Patients

|  |  |  |
| --- | --- | --- |
| **Treatment-emergent Adverse Event** | **Number of Patients (%) in the Safety Analysis** | |
| **TER, n = 894** | **OxyContin, n = 223** |
| Constipation | 202 (22.6) | 86 (38.6) |
| Nausea | 162 (18.1) | 74 (33.2) |
| Somnolence | 133 (14.9) | 25 (11.2) |
| Dizziness | 132 (14.8) | 43 (19.3) |
| Headache | 119 (13.3) | 17 (7.6) |
| Fatigue | 87 (9.7) | 23 (10.3) |
| Vomiting | 63 (7.0) | 30 (13.5) |
| Pruritus | 48 (5.4) | 23 (10.3) |

Among patients reporting constipation, the mean (SE) change in PAC-SYM score from baseline was lower in the TER patients (0.3 [0.05]) than those in the OxyContin group (0.5 [0.14]).

Within 3 days of the last dose of study medication, 1.5% (13) of the TER group and 0.9% (2) of the OxyContin group reported TEAE “withdrawal syndrome.” All COWS scores for all time periods were <25 (“mild” severity). For the 147 COWS assessments completed >2 to 4 days after opioid discontinuation, the majority of patients in both treatment groups had no opioid withdrawal (TER, 77.6% [97/125]; OxyContin, 72.7% [16/22]). Among patients with COWS assessments that were completed >5 days after treatment discontinuation, 88% (146/166) in the TER group and 84% (42/50) in the OxyContin group reported no opioid withdrawal. Mean SOWS total scores from 2 to ≥5 days after discontinuation of study medication ranged from 6.9 to 9.5 for patients treated with TER and from 7.5 to 12.3 for patients treated with OxyContin.

Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain*. 2007;23(4):287-299.

Location: 35 centers in US; Study Dates: Aug 1998-Feb 2002

An open-label, uncontrolled, multi-center, prospective, longitudinal, registry study evaluated selected long-term outcomes associated with OxyContin therapy for up to 3 years for non-cancer pain.

Eligibility criteria for this open-label extension trial included participation in one of five controlled trials, with protocol-specified maximum daily exposure of 80-160 mg OxyContin, of low back pain, osteoarthritis pain, or painful diabetic neuropathy. Completers, aged 18 years or older, who continued to require opioid analgesia for pain of moderate to severe intensity were offered enrollment into the registry extension study. The protocol specified following each patient for three years, but for administrative reasons it was terminated before all subjects had completed three years of observation.

The study enrolled 233 patients. In the prior controlled clinical trials, 117 patients (50%) received OxyContin, 60 (26%) received an immediate-release oxycodone- or hydrocodone-acetaminophen combination product, and 56 (24%) received placebo. Patients who were already taking OxyContin within the two weeks preceding registry baseline continued with their last stable dose regimen. All other patients received a starting dose of 10 mg OxyContin. Titration, up or down, could be performed at any point during the registry study, based on clinical assessment, but no more than once every seven days until stable pain control was achieved for 48 hours. Asymmetric dosing (ie, AM dose ≠ PM dose) was allowed if pain was typically greater during the day or night. All OxyContin dosing was every 12 hours. Breakthrough pain was managed with the use of additional analgesic medication at the discretion of the investigator.

The intent-to-treat (ITT) population comprised those patients who took at least one dose of OxyContin and provided at least one post-dose observation. Data from the ITT population (n=219; mean age, 55.9 years [SD±13.2]; female, 57%) included dose, pain severity, and treatment acceptability. Safety data were analyzed in all 227 patients who received at least one OxyContin dose. Up to and including premature termination, 61 patients were dismissed from the study by the site (n=8) or the sponsor (n=53).

Data collected at 3-month intervals included the daily OxyContin dose; the average pain intensity, assessed by the Brief Pain Inventory (BPI) numerical rating scale (NRS), which is an 11-point, interval scale where 0=no pain and 10=pain as bad as you can imagine; treatment acceptability, evaluated with a 6-point rating scale (1=not acceptable and 6=totally acceptable); incidence and severity of adverse events (AEs); and physician- investigator assessments of problematic drug-related behavior.

At registry entry, the daily OxyContin doses of the ITT patients were <20 mg (n=31), 20 to 39 mg (n=114), 40 to 59 mg (n=40), 60 to 79 mg (n=6), 80 to 99 mg (n=17), and ≥100 mg (n=11), with the mean (± SD) being 34.6±29.2 mg. The need for opioid titration was greatest in the first three months of participation in the registry study, with 44% of patients requiring some increase in daily dose. After month 3, the need for dose escalation generally declined, with 23% requiring some daily dose increase during months 4 to 6, 17% during months 10 to 12, and approximately 10% (range, 8-13%) for each time interval thereafter. The overall mean (± SD) daily OxyContin dose for all patients across all time points was 52.5±38.5 mg (range, 10 to 293.5 mg). The duration of OxyContin exposure, in years, for the 219 ITT patients was: at least one (n=141), at least two (n=86), and three years (n=39). The mean (± SD) duration of OxyContin dosing was 541.5±370 days.

The patients’ BPI average pain intensity scores declined after treatment with OxyContin (5.1±2.2, baseline vs. 4.4±2.1, end of month 3), with the fraction of ITT patients rating their average pain intensity as ≥7 (“severe” on BPI) decreasing from 31% to 16%. At the end of month 3, 52% of ITT patients rated their average pain intensity from 0 to 4 (“mild” on BPI). After month 3, 56% of the patients never had an increase in pain exceeding 2 points on the 11-point scale. Acceptability of OxyContin increased from baseline to a little over 4 on the 6-point scale and remained elevated, relative to baseline, throughout the duration of participation in the study.

Of the safety population (n=227), 200 patients, or 88%, reported AEs. In 110 patients, or 48.5%, the AEs were considered by the investigator to be related to OxyContin. Of those considered related to OxyContin, most frequently reported AEs (at least 2% of the population) were constipation (15%), nausea (12%), somnolence (8%), vomiting (7%), and depression (2%). By the end of month 3, the incidence of these AEs declined substantially, except for depression. Forty-one patients (18%) discontinued participation related to AEs, with constipation and nausea being the most common reasons for discontinuation. Serious AEs were reported in 63 patients, including 7 deaths (n=5, known, pre-existing chronic illnesses; n=1, likely related to a known drug- drug interaction [oxycodone, phenylpropanolamine, and ethanol]; n=1, probable trauma).

Site investigators identified 13 patients with potentially-problematic drug-related behavior. Following review of all available information by the independent, expert panel, six (2.6% of the safety population) were identified as having signs of possible drug abuse or dependence.

Nicholson B, Ross E, Sasaki J, Weil A. Randomized trial comparing polymer-coated extended-release morphine sulfate to controlled-release oxycodone HCl in moderate to severe nonmalignant pain. *Curr Med Res Opin*. 2006 Aug;22(8):1503-14.

Location: 5 study centers in the US

A 6-month, phase IV, prospective, multi-center, randomized, open-label, blinded endpoint study compared the efficacy, tolerability, and safety of morphine sulfate extended-release (MSER) and controlled-release oxycodone (CRO) in the long-term treatment of chronic, moderate to severe, non-cancer pain. Neuropathic pain was excluded. Patients (age, 18-85 years) with a baseline pain score ≥4 on an 11-point scale from the Brief Pain Inventory (BPI) were eligible for participation in the study.

Patients were randomized to either CRO or MSER, with starting doses of CRO (administered morning and evening, every 12 hours) and MSER (administered once every morning) determined by the investigator, based on the patient’s previous analgesic regimen. Patients attended seven clinic visits over a 6-month period (weeks 0 [baseline], 1, 2, 4, 8, 12, and 24). During clinic visits, clinicians were permitted to increase the dose (if not increased during previous visits) or increase the dosing frequency to twice daily for MSER or three times daily for CRO (if the dose was increased during previous visit). The thrice-daily option for CRO is not consistent with the Full Prescribing Information for OxyContin, nor is it supported by well-controlled clinical trials. Between the week 12 and week 24 visits, the clinician was permitted to adjust dosing as clinically indicated.

Five efficacy endpoints, as shown in **Table 23**, and adverse events (AEs) were assessed during the course of the study.

#### Table 23. Efficacy Outcomes

|  |  |
| --- | --- |
| **Endpoint** | **Measurement** |
| **Quality of Life** | Change from baseline at weeks 4 and 24 on the Physical (PCS) and Mental (MCS) Component Summary scores of the 36-Item Short-Form Health Survey, version 2 (SF- 36v2) |
| **Pain** | Change in pain intensity from baseline at weeks 2, 4, 8, 12, and 24 on the 11-point BPI scale, with a 2-point improvement defined as a ‘clinically meaningful’ change. |
| **Sleep** | Change in sleep quality from baseline at weeks 2, 4, 8, 12, and 24 on the 11-point BPI ‘pain interference with sleep’ scale (0 = “does not interfere,” 10 = “completely interferes”) |
| **Patient Global Assessment** | Change in patient’s global assessment of current therapy score from baseline at weeks 2, 4, 8, 12 and 24 on a multifactorial, 9-point scale: -4 = “completely dissatisfied, uncontrolled pain, cannot function, disruptive dosing schedule,” 0 = variable satisfaction with ‘slight satisfaction’ days approximately equal to ‘slight dissatisfaction’ days, and +4  = “completely satisfied, pain controlled, no side effects, convenient schedule” |
| **Clinician Global Assessment** | Change in clinician’s global assessment of current therapy score from baseline at weeks 4 and 24 on a different multifactorial, 9-point scale: -4 = “completely dissatisfied, consider change to different drug/class,” 0 = “variable satisfaction,” and +4 = “completely satisfied, no change to dose or schedule, no side effects” |

Of the 112 randomized patients, 108 patients (n=50, CRO; n=58, MSER) comprised the safety population (took at least one dose of study medication), while the intent-to-treat (ITT) population included 97 patients (mean age, 51.3 years; age range, 20-83 years) who took at least one dose of CRO (n=59) or MSER (n=53) and had at least one valid post-baseline assessment.

Baseline demographics were similar between the two groups, but the MSER group included significantly more females (62.8%, MSER vs. 40.7%, CRO; p<0.05) and had significantly lower mean Physical Component Summary scores on the SF-36v2 at baseline (26.4 vs. 31.1, respectively; p<0.05).

Pain scores significantly decreased from baseline to week 24 with both treatments (p<0.05). Pain score with CRO decreased from 7.4 at baseline to 6.0 at week 24, while pain scores with MSER decreased from 7.2 at baseline to 5.3. The difference between the decreases in the two arms was not significant. Treatment with MSER achieved the ‘clinically meaningful’ decrease (2-points) at week 8 (-2.1) and week 24 (-2.0). The starting mean daily dose of CRO was 34.0±22.63 mg and increased to 84.7±66.14 mg at study completion. The mean daily dose for MSER increased from 30.0±27.18 mg at the start of the study to 78.7±55.62 mg at the end of the study.

Both treatment groups demonstrated significantly improved sleep scores from baseline at each assessment visit. At week 24, the mean change from baseline with MSER was greater than with CRO (p<0.05), as was the mean sleep score at week 24. CRO sleep scores decreased from 6.4 at baseline to 4.8 at week 24, while MSER was associated with a change from 6.1 at baseline to 3.5.

The baseline difference in mean PCS scores persisted throughout, but both CRO and MSER treatments lead to significantly increased PCS scores by week 24 (p<0.05). While there was no significant difference between treatments in mean MCS scores at weeks 4 and 24, scores continued to improve throughout the trial. By week 24, CRO treatment was associated with a significant improvement in mean MCS score compared to baseline (p<0.05).

Baseline patient global assessment of current therapy scores were -1.4 in those randomized to receive CRO and -2 for those randomized to the MSER arm. Beginning at week 2 and continuing through week 24, both treatment groups reported significantly greater satisfaction with their study medications (change from baseline to week 24: +1.7, CRO and +2.6, MSER; p<0.001, both treatments vs. baseline). Physicians’ global assessment of therapy also improved significantly from baselines of -2.0, CRO and -2.2, MSER to +3.1 for CRO and +4.0 for MSER. There was no significant difference in scores between treatment groups.

Sixty-six patients (61%) experienced AEs, including 47 in whom the AE was judged as being treatment-related (**Table 24**). Typical opioid side effects predominated, with most instances being of mild to moderate in intensity. CRO treatment was associated with a significantly lower rate of constipation (p=0.043). A total of 28 patients (n=15, MSER and n=13, CRO) discontinued therapy due to an AE, most frequently related to a gastrointestinal condition (nausea and constipation) or a nervous system disorder. Twelve patients experienced a serious AE, one of whom experienced a change in mental status that was considered to be related to treatment with MSER. No deaths occurred during the course of this study.

#### Table 24. Treatment-related Adverse Events (TRAEs) Occurring in ≥3% of Patients

|  |  |  |
| --- | --- | --- |
| **Treatment-related Adverse Event** | **Number of Patients (%) in the Safety Analysis** | |
| **MSER, n=50** | **CRO, n=58** |
| Constipation | 13 (26.0) | 6 (10.3)\* |
| Nausea | 7 (14.0) | 8 (13.8) |
| Somnolence | 5 (10.0) | 4 (6.9) |
| Cognitive disorder | 2 (4.0) | 1 (1.7) |
| Fatigue | 2 (4.0) | 1 (1.7) |
| Headache | 2 (4.0) | 0 (0.0) |
| Dizziness | 1 (2.0) | 3 (5.2) |
| Peripheral edema | 0 (0.0) | 2 (3.4) |
| Sedation | 0 (0.0) | 3 (5.2) |

\*p=0.043

Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Arch Intern Med*. 2000;160(6):853- 860.

See [summary](#_bookmark17) in section 3.1.1, Studies in Patients with Osteoarthritis-related Pain.

#### Safety and Efficacy in Opioid-tolerant Pediatric Patient Population

**An Open-label, Multicenter Study of the Safety of Twice Daily Oxycodone Hydrochloride Controlled- release Tablets in Opioid Experienced Children From Ages 6 to 16 Years Old, Inclusive, With Moderate to Severe Malignant and/or Nonmalignant Pain Requiring Opioid Analgesics (OTR3001)**

Location: 44 study center locations in 8 countries (US, Israel, Greece, Guatemala, Hungary, New Zealand, Spain, UK). **Clinical Trials.gov Identifier**: NCT01192295

While the safety, efficacy, and pharmacokinetics of OxyContin were evaluated in an open-label clinical trial of opioid-tolerant pediatric patients aged 6 to 16 years, there were insufficient numbers of patients less than 11 years of age enrolled in this study to establish the safety of the product in this age group. The safety and efficacy of OxyContin have been established only in pediatric patients ages 11 to 16 years (OxyContin FPI).

#### Trial Design and Entry Criteria

This was a phase 3, multicenter, open-label clinical trial of opioid-tolerant pediatric patients with moderate to severe chronic pain. The primary objective was to characterize the safety of OxyContin in opioid-tolerant pediatric patients. The secondary objectives were to characterize the efficacy of OxyContin and provide additional pharmacokinetic data in this population. The trial consisted of three phases; screening, 2-4 weeks of open-label treatment, and follow-up.

Patients that qualified for the screening process included those that:

* + were at least 6 years and less than 17 years of age
  + had moderate to severe malignant or nonmalignant pain, where an opioid analgesic was required on an ongoing, around-the-clock basis
  + were opioid-tolerant having been treated with opioids for at least the 5 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 the start of OxyContin dosing
  + were willing and able to swallow tablets whole
  + were able to understand and complete the age-appropriate scale to rate pain intensity
  + had a parent/caregiver who could perform study assessments
  + did not meet any exclusion criteria (eg, allergy to oxycodone or other opioids, surgery within 5 days prior to dosing, underlying condition that might predispose patient to gastrointestinal obstruction, being maintained on methadone for pain)

Patients who met all eligibility criteria at screening could enter into open-label treatment. Upon entering the open-label treatment period, patients discontinued all other around-the-clock opioid medications and were initiated on a dose of OxyContin based on the dose of their previous opioid. Patients could be treated with a total daily dose ranging between 20- to 240-mg of OxyContin administered in divided doses every 12 hours for a minimum of 2 weeks and up to 4 weeks. Supplemental short-acting opioid and nonopioid pain medication was permitted during the study as deemed appropriate by the investigator.

Upward or downward dose titration was permitted. Upward titration could only occur after 48 hours of OxyContin treatment at a particular dose. Dose increases were calculated based on a patient’s use of supplemental pain medication. The maximum dose for a single upward titration was 25% of the patient's current dose. Downward adjustments could be made at any time. Patients needed to be taking a minimum dosage of OxyContin 20 mg daily to remain in the study.

#### Clinical Outcome(s)/Measures

Primary

Safety assessments consisted of adverse events (AEs), physical examinations, clinical laboratory evaluations, vital signs, pulse oximetry, and somnolence using the University of Michigan Sedation Scale (UMSS).

Secondary

Efficacy assessments consisted of the following:

* Pain right now assessed by patients at time of dosing using the Faces Pain Scale-Revised (FPS-R), for patients aged 6 to <12 years
* Pain right now assessed by patients at time of dosing using the 100-mm Visual Analogue Scale (VAS), for patients aged 12 to 16 years
* Use of supplemental pain medication
* Parent/caregiver-assessed Functional Disability Inventory (FDI) at baseline, week 2 and week 4/early discontinuation, and
* Parent/caregiver-assessed Global Impression of Change (PGIC) at the final visit.

Pharmacokinetic assessments were done at screening, week 2, and week 4 or when the patient discontinued the trial.

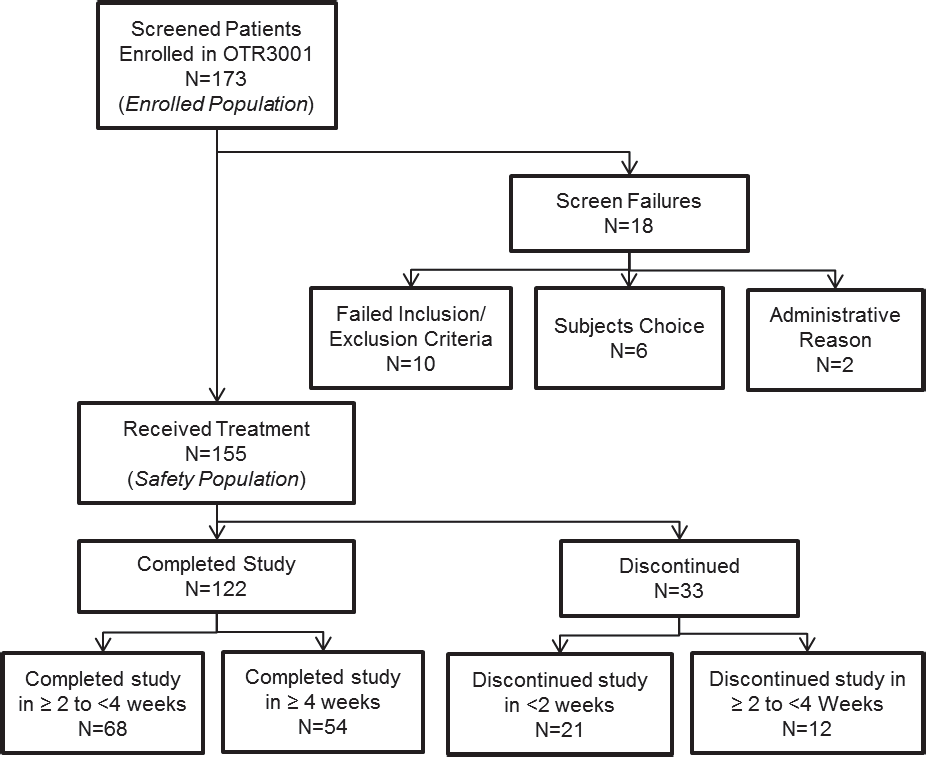
Study population characteristics, efficacy data, and safety data were summarized overall and by age group (ages 6 to <12 years and ages 12 to 16 years).

#### RESULTS

**Patient Disposition**

A patient was considered as completing the study if they completed at least 2 weeks of OxyContin dosing and did not need additional treatment with opioid medication for pain relief or if the patient completed the entire 4 weeks of OxyContin treatment. The safety population consisted of 155 patients and of these 122 patients (78.7%) completed the study. **Figure 7** presents patient disposition from screening to study completion/discontinuation.

#### Figure 7. Patient Disposition



Of the 155 patients in the overall safety population, 21(13.5%) discontinued from the study with <2 weeks of OxyContin treatment and 12 (7.7%) patients discontinued from the study with 2 to <4 weeks of OxyContin treatment. The most common reasons for discontinuation were adverse events, subject’s choice, and administrative.

#### Demographics and Numbers Studied

The safety population consisted of 155 patients with similar percentages of male and female patients (42.6% vs 57.4%, respectively); 69.7% of subjects were white. **Table 25** presents basic demographic information by age group.

#### Table 25. Safety Population: Demographics and Numbers Studied

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Age Group** |  |
|  | **6 to <12 Years (N=27)** | **12 to 16 Years (N=128)** | **Total (N=155)** |
| **Age (years)** Mean (SD) Median Range | 9.6 (1.65)  10.0  6-11 | 14.5 (1.34)  15.0  12-16 | 13.7 (2.33)  14.0  6-16 |
| **Sex, n (%)** Male Female | 13 (48.1)  14 (51.9) | 53 (41.4)  75 (58.6) | 66 (42.6)  89 (57.4) |
| **Screening BMI (kg/m 2)**  Mean (SD) Median Range Missing | 19.08 (2.775)  18.57  14.2-27.1  3 | 22.92 (5.639)  21.92  12.2-44.7  0 | 22.32 (5.468)  21.21  12.2-44.7  0 |

The pain conditions in patients studied included surgery (N=88), cancer (N=24), sickle cell disease (N=17), other pain conditions (N=11), rheumatologic conditions (N=5), fracture (N=5), and trauma (N=5). Patients with surgical pain had surgery due to cancer, an orthopedic condition, or trauma. Other pain conditions included diagnoses of abdominal pain, fibromyalgia, pelvic/hip pain, trigeminal neuralgia, or reflex sympathetic dystrophy.

The opioid medications most frequently used in the 5 days prior to starting OxyContin (used by ≥ 5% of patients overall) were oxycodone, hydromorphone, morphine, hydrocodone, fentanyl, or remifentanil.

#### Safety

Dosing and Extent of Exposure

The mean daily dose of OxyContin was 33.3 mg/day. For all age groups, OxyContin dose from week 1 to week 4 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 was 20.7 (range: 1-43 days) and was similar for both age groups. In an extension study, 23 of the 155 patients who completed 4 weeks of treatment in the core study and were deemed appropriate for continued treatment with OxyContin in the opinion of the study physician were treated beyond four weeks, including 13 who were treated for 28 weeks.

Adverse Events

Treatment-emergent AEs (TEAEs) were reported for 108 patients (69.7%), with similar rates in both age groups. **Table 26** presents TEAEs that occurred in at least 5% of patients.

There were 4 (2.6%) deaths, all in patients who had malignant neoplasm. Their deaths were not considered to be related to OxyContin. A total of 24 (15.5%) patients experienced serious adverse events (SAEs). No more than 6 patients experienced any individual SAE.

#### Table 26. Incidence of TEAEs Reported in 5% of Patients in the Safety Population

|  |  |  |  |
| --- | --- | --- | --- |
| **Age Group** | | | |
|  | **6 to <12 Years** | **12 to 16 Years** | **Total** |
| **MedDRA System Organ Class Preferred Term** | **(N = 27)**  **n (%)** | **(N = 128) n (%)** | **(N = 155) n (%)** |
| Any TEAE | 19 (70.4) | 89 (69.5) | 108 (69.7) |
| **Gastrointestinal disorders** | 12 (44.4) | 51 (39.8) | 63 (40.6) |
| Vomiting | 6 (22.2) | 28 (21.9) | 34 (21.9) |
| Nausea Constipation Diarrhea  **General disorders and administration site conditions** Pyrexia  **Nervous system disorders**  Headache | 3 (11.1)  4 (14.8)  3 (11.1)  9 (33.3)  6 (22.2)  3 (11.1)  3 (11.1) | 20 (15.6)  12 (9.4)  5 (3.9)  28 (21.9)  12 (9.4)  36 (28.1)  19 (14.8) | 23 (14.8)  16 (10.3)  8 (5.2)  37 (23.9)  18 (11.6)  39 (25.2)  22 (14.2) |
| Dizziness | 0 | 12 (9.4) | 12 (7.7) |
| **Skin and subcutaneous tissue disorders** | 4 (14.8) | 22 (17.2) | 26 (16.8) |
| Pruritus | 3 (11.1) | 7 (5.5) | 10 (6.5) |
| Abbreviations: TEAE = treatment-emergent adverse event; MedDRA = Medical Dictionary for Regulatory Activities | | | |

Somnolence

Two older patients had a UMSS score of 3 after the first dose of OxyContin. A UMSS score of 3 indicates a patient who is in deep sleep that arouses to deeper physical stimulus (range 0-4, 0 = awake and alert, 4 = unarousable). There were no other UMSS scores ≥ 3 reported during the trial.

Other Clinical Evaluations Related to Safety

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 (1 from each age group) had a clinically significant pulse oximetry finding. Neither event resulted in dose reduction or discontinuation.

#### Efficacy

Average Pain Right Now Scores

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, alone or in combination with supplemental analgesics, reduced or maintained pain right now scores from baseline to week 4.

Supplemental Pain Medication

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.

Functional Disability Inventory and Global Impression of Change

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.

#### Pharmacokinetics

Pharmacokinetic data was obtained from 105 patients in this trial. In the pediatric age group of 11 years of age and older, systemic exposure of oxycodone is expected to be similar to adults at any given dose of OxyContin.

## shed and Unpublished Data and Clinical Studies Supporting Off-Label Indications

#### Pre-emptive Analgesia

Illgen RL, Pellino TA, Gordon DB, Butts S, Heiner JP. Prospective analysis of a novel long-acting oral opioid analgesic regimen for pain control after total hip and knee arthroplasty. *J Arthroplasty*. 2006;21(6):814-820.

See [summary](#_bookmark25) in section 3.1.1, Studies in Patients with Postoperative Pain.

Kampe S, Warm M, Kaufmann J, et al. Clinical efficacy of controlled-release oxycodone 20mg administered on a 12-h dosing schedule on the management of postoperative pain after breast surgery for cancer. *Curr Med Res Opin*. 2004;20(2):199-202.

See [summary](#_bookmark26) in section 3.1.1, Studies in Patients with Postoperative Pain.

#### Acute Herpes Zoster

Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain*. 2009;142:209-217.

Location: Houston, TX and Rochester, NY

A randomized, double-blind, placebo-controlled trial in patients with acute pain due to herpes zoster assessed the safety and tolerability of controlled-release (CR) oxycodone compared to gabapentin or placebo.

Adult patients (≥ 50 years of age) with herpes zoster rash onset within 6 calendar days and worst pain in the past 24 hours rated as ≥3 on a 0-10 numerical rating scale (NRS; 0=no pain, 10=worst possible pain) were randomized to oxycodone CR, gabapentin, or placebo.

At the randomization visit, patients (N=87) began open-label treatment with an antiviral agent, famciclovir, and were randomized using a double-dummy design to receive either oxycodone CR (n=29), gabapentin (n=29), or placebo (n=29) for 28 days. Patients were titrated to maximum allowable daily doses of oxycodone CR and gabapentin, 120 mg and 1800 mg, respectively (see **Table 27**). Six study visits were scheduled at baseline, days 4, 8, 14, 28 and 35. Patients were treated according to a three-tier rescue medication protocol for unacceptable pain where first tier consisted of acetaminophen (APAP ) at baseline, second tier ibuprofen on day 4, and third tier placebo or oxycodone/APAP on day 8. After titration, if rescue was still needed, all subjects received open-label oxycodone/APAP. All subjects were given docusate sodium-senna concentrate tablets at baseline visit with instructions to take if constipation develops.

#### Table 25. Titration Schedule for Oxycodone CR and Gabapentin

|  |  |  |
| --- | --- | --- |
| **Day** | **Oxycodone CR** | **Gabapentin** |
| 1 | 10 mg OR 10 mg every 12 h | 300 mg at bedtime |
| 2 | 10 mg every 12 h | 300 mg in the morning, 300 mg at bedtime |
| 3 | 10 mg in the morning, 20 mg 12 h later | 300 mg every 8 h |
| 4 | 20 mg every 12 h | 300 mg in the morning, 300 mg 8 h later, 600 mg 8 h later |
| 5 | 30 mg every 12 h | 300 mg in the morning, 300 mg 8 h later, 600 mg 8 h later |
| 6 | 40 mg every 12 h | 600 mg in the morning, 300 mg 8 h later, 600 mg 8 h later |
| 7 | 50 mg every 12 h | 600 mg in the morning, 300 mg 8 h later, 600 mg 8 h later |
| 8-28 | 60 mg every 12 h | 600 mg every 8 h |

The primary measure used to assess the tolerability and safety of oxycodone CR and gabapentin was non- completion of the trial. A secondary objective of the study was to examine the efficacy of oxycodone CR and gabapentin for reducing acute pain in herpes zoster when used in combination with an antiviral agent. Outcome variables assessed were the averages of the worst pain intensity ratings calculated from the daily diaries over days 1-8, days 1-14, and days 1-28. Subjects rated their average and worst pain “since rash onset” at baseline and their worst pain “during past day” everyday using a 0-10 NRS. Additionally, the Short- form McGill Pain Questionnaire (SF-MPQ) assessed the sensory and affective dimensions of pain, and Brief Pain Inventory (BPI) Interference Scale assessed impact of pain on patient’s quality of life.

Eight (27.6%) patients in the oxycodone CR group, 5 (17.2%) in the gabapentin group, and 2 (6.9%) in the placebo group did not complete the trial (p=0.02, oxycodone CR vs. placebo; p=0.11, gabapentin vs. placebo). Dropouts in the oxycodone CR and gabapentin groups were mostly due to adverse events (AEs) or serious AEs, mainly constipation and dizziness, respectively. The number-needed-to-harm for discontinuing participation in the trial because of an AE or serious AE was 5.8 for oxycodone CR compared to 9.7 for gabapentin.

Treatment with oxycodone CR significantly reduced the average worst pain over days 1-8 (p=0.01) and days 1- 14 (p=0.02) relative to placebo. Average worst pain results for days 1-28 were consistent with a benefit of oxycodone CR compared to placebo, but were not statistically significant (p=0.14). Treatment with gabapentin

did not show greater efficacy over placebo in any observation period. The numbers-needed-to-treat for clinically meaningful pain relief (≥30% pain reduction from baseline) over days 1-14 was 2.9 for oxycodone CR and 9.6 for gabapentin. No significant change in quality of life measures were reported for any group during any assessment period. Although not significantly different amongst the three groups, there was less use of all three tiers of rescue analgesia in the oxycodone CR group compared to gabapentin and placebo groups. Sixty-nine percent of patients in the oxycodone CR group, 31% of patients in the gabapentin group, and 44.8% of patients in the placebo group used docusate sodium-senna concentrate tablets.

At least one AE was reported by 85.1% of subjects enrolled in the trial (75.9%, oxycodone CR vs. 93.1%, gabapentin vs. 86.2%, placebo). Four subjects experienced serious AE (oxycodone CR: disorientation and dehydration [n=1] and pre-syncope [n=1]; gabapentin: fever [n=1]; placebo: congestive heart failure [n=1]). AEs with the greatest differences in incidence between oxycodone CR or gabapentin and placebo were common side effects of these medications, including constipation, dizziness, drowsiness, emesis, nausea, and sedation.

## Evidence Table Spreadsheets of all Published and Unpublished Studies

**Table 28** includes the summaries of all OxyContin safety and efficacy studies.

#### Table 28. Summary of OxyContin Safety and Efficacy Studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Mucci-LoRusso P, Berman BS, Silberstein PT, et al. Controlled- release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *Eur J Pain.* 1998;2(3):239-  249. | OxyContin q12h  MS Contin q12h  Dose titrated to stable pain control | N=100  OxyContin, n=48  MS Contin, n=52 | 12 days | * Patients requiring 30- 340 mg oral oxycodone daily * Patients on maximally labeled doses of non-opioid analgesics who, in the investigator’s judgment, would require   >30 mg oral oxycodone daily | * History of sensitivity to oxycodone or morphine * Contraindication for opioid therapy * Severely compromised organ function | Multi-center, Randomized, Double-blind, Double- dummy, Parallel | Primary:   * Pain intensity * FACT-G (QOL) * Acceptability of therapy   Secondary:   * PK/PD * Safety | * Compared to baseline, both groups achieved significant improvements in pain intensity (p≤0.005) and acceptability of therapy (p=0.0001, OxyContin; p=0.0061, MS Contin). * FACT-G QOL scores remained stable for both groups. |
| Kaplan R, Parris WCV, Citron ML, et al. Comparison of controlled- release and immediate- release oxycodone tablets in patients with cancer pain. *J Clin Oncol.*  1998;16(10):3230  -3237. | OxyContin q12h  IR oxycodone | N=164  OxyContin, n=81  IR  oxycodone, n=83 | 5 days | * Patients with chronic cancer pain being treated with a strong single-entity opioid or >10 tablets of a fixed combination opioid/non- opioid analgesic | * Patients receiving any other analgesics * Patients scheduled to receive radiotherapy immediately before or during the study * The above criteria were later eliminated to facilitate enrollment | Double-blind, Repeated- dose, Parallel | Primary:   * Pain intensity (0-3 CAT) * Acceptability of therapy (1-5 CAT)   Secondary:   * PK/PD * Safety | * There were no significant differences between treatment groups in pain intensity (slight) and acceptability of therapy (p>0.05). |
| Citron ML, Kaplan R, Parris WCV, et al. Long-term administration of controlled-release oxycodone tablets for the treatment of cancer pain.  *Cancer Invest.*  1998;16(8): 562-  571. | OxyContin q12h, variable (no maximum) | N=87  Parris et al., n=30  Kaplan et al., n=57 | 12 weeks  (3 months) | * Patients who had previously participated in Parris et al., 1998 and Kaplan et al., 1998 | * History of adverse reactions following opioids and certain centrally- acting drugs or cimetidine * Hypersensitivity to oxycodone * Paralytic ileus * Compromised organ function | Usual-use, Open-label, Safety and Efficacy Extension | Primary:   * Pain intensity (4-point CAT scale, none to severe) * Acceptability of therapy (5- point CAT scale, very poor to excellent)   Secondary:   * PK/PD * Safety | * At baseline and throughout the 12 weeks of the study, overall mean pain-intensity scores were slight to moderate, acceptability of pain scores were fair to good, and these scores did not differ significantly from week to week. * There was a significant decrease in the number of patients with opioid- related adverse events over time (55%, Week 1 vs. 13%, Week 12; p=0.0002), while stable pain control was maintained. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Bercovitch M, Adunsky A. High dose controlled- release oxycodone in hospice care. *J Pain Palliat Care Pharmacother*. 2006;20(4):33-39. | OxyContin, variable | N=97  Low-dose (<30 mg/day), n=34  Moderate- dose (31-150 mg/day), n=45  High-dose (>150  mg/day), n=18 | 2 years | * End-stage cancer patients in an inpatient hospice | Exclusions not reported | 2-year, Retro- spective, Parallel group | * Pain intensity via VAS/NRS * Quality of Life (sleep/mood) * Use of rescue analgesia * AEs | * Mean daily doses (mg): 19.4±1.4, low-dose; 62.2±28.3, moderate- dose; 231±74.9, high-dose * Painful bony metastases were significantly correlated with high doses of OxyContin (p=0.008). * The degree of pain was significantly correlated with being in the higher dose group (p=0.039). * Use of rescue medication was limited; no significant difference amongst the OxyContin groups (9%, low-dose vs. 12%, moderate- dose vs. 10%, high-dose). * No significant differences in sleep quality or mood were observed; however, for at least half of the study duration, patients in the moderate- and high-dose groups maintained Karnofsky scores >40 points (OR=3.77, CI 1.1-13.0 and OR=4.95, CI 0.8-29.9, respectively). * No significant differences in AEs aside from dry mouth, which was reported more frequently by patients receiving low-dose OxyContin (p=0.014). |
| Ferrares F, Becchimanzi G, Bernardo M, et al. Pain treatment with high-dose, controlled-release oxycodone: an Italian perspective. *Ther Clin Risk Manag.* 2008;4(4):665-  671. | CRO, variable | N=227 | 3 months | Age, >18 years   * Baseline pain intensity score >4 per NRS * Able to take oral medication | * Current radiotherapy treatment * Modification of adjuvant medications required * Intolerant to oxycodone | 3-month, Open-label, Multicenter, Observational | * Pain intensity * AEs | * Mean daily CRO dose: 221.84 mg * Mean duration of CRO therapy:   37.24 days   * With CRO therapy, the mean NRS score significantly improved from baseline to study end (7.73 vs. 2.85, p<0.00001). * AEs, including constipation, nausea, and vomiting, were reported by 39.64% of patients, but did not result in study discontinuation. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Li X-M, Liu D-Q,  Wu H-Y, Yang C, Yang L. Controlled- release oxycodone alone or combined with gabapentin for management of malignant neuropathic pain. *Chin J Cancer Res*. 2010;  22(1):80-86. | Phase I: CRO  q12h,variable  Phase II: (starting Day 8)   * Pain score   <4: CRO  q12h   * Pain score   ≥4: OxyContin + gabapentin (OG); dose of OxyContin kept constant; gabapentin doses: <60 years of age, 300 mg TID;  >60 years of  age, 100 mg TID; max dose=3200 mg | N=63 | 3 weeks  Phase I: day 0-day 8  Phase II: day 8-day 22 | Age, 18-80 years   * Moderate or severe neuropathic cancer pain (active cancer lesion causing the pain by infiltration/ compression of nervous structures or neuropathy due to chemo- therapy) * Pain intensity score ≥4 on NRS in 24h prior to screening * Life expectancy   ≥30 days   * Karnofsky performance status ≥40 | * Unable to take oral med * SCr>1.5 mg/mL or CrCl<60 mL/min * Current opioid, gabapentin, nonopioid analgesics, and other adjuvant drug use * Chemotherapy 7 days before screening Radiotherapy to pain-   producing lesion within 15 days of screening | Single-center, Open-label, Observational | * Pain intensity per numerical rating scale (NRS; 0-10)   + Analgesic doses (mean daily dose;MDD)   + AEs | Phase I:   * Mean pain intensity score significantly decreased with OxyContin by day 8 [7.91(1.29), baseline vs. 3.74 (1.11), CRO; p<0.001]   CRO MDD: 62.64(32.35) mg, day 8  Phase II:   * CRO monotherapy (n=22) Mean pain intensity score significantly decreased from day 8 to day 15 (2.62 vs. 2.00, respectively; p=0.004); decrease not significant from day 15 to day 22. * OG (n=36) Mean pain intensity score significantly decreased from day 8 to day 15 (4.47 vs. 2.94, respectively; p<0.001); mild improvement from day 15 to day 22. * MDD of CRO monotherapy: significantly increased by day 15 (71.43[26.51] mg; p=0.021) and day 22 (81.90[32.80] mg; p=0.004) * OG - Gabapentin MDD: significantly larger dose at day 22 than that at day 15 (993.75[279.33] vs. 862.50[282.56]; p<0.001). * No severe side effects observed * Most common AE in all patients: constipation (13.64%, CRO vs. 14.26%, OG). Other AEs included nausea, vomiting, dizziness, sedation, sweating, pruritus, dry mouth, asthenia, and ataxia. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Mercadante S, Ferrera P, David F, Casuccio A. The use of high doses of oxycodone in an acute palliative care unit. *Am J Hosp Palliat Care*. 2011;28:242-244. | CRO, variable | N=212  Low-dose (<120 mg/d), n=129;  Moderate- dose (120-  240 mg/d), n=43; High- dose (>240 mg/d), n=40 | 3 years | * Adult patients with cancer pain who were admitted to an acute palliative care unit | Exclusions not reported | 3-year, Retrospective Chart review | * Pain intensity via NRS * AEs | * Overall mean CRO dose: 141±167 mg (range, 10-960 mg) * Mean CRO doses per treatment group (mg): 48.4±25, low dose; 156.5±30.5, moderate-dose; 435±196, high-dose * Doses were significantly lower in older patients (p<0.0005). * At hospital discharge, mean pain intensity was 2.9±1.9. * AEs were deemed mild and unrelated to CRO doses by investigators; specific AE were not reported |
| Ravera E, Di Santo S, Bosco R, Arboscello C, Chiarlone R. Controlled- release oxycodone tablets after transdermal- based opioid therapy in patients with cancer and noncancer pain. *Aging Clin Exp Res*. 2011;23(5-  6):328-332. | OxyContin q12h, variable | N=41 | 21 days | * Patients persistent cancer and noncancer pain * Current treatment with transdermal opioid therapy for   ≥5 days | Exclusions not reported | Multi-center, Open-label, Observational | Primary:   * Change in pain intensity per NRS score (0=no pain and 10=maximum severity) from T0 to day 3, day 7, and day 21   Secondary:   * QOL | * Mean daily dose of OxyContin:   68.75 mg at beginning of study; increased and stabilized to 72.39 mg at day 7 through end of study   * After 3 days of OxyContin treatment, average pain intensity significantly decreased by 38.3% (p<.001). * A significant decrease in NRS pain intensity scores was maintained through day 21 (-65.75%; p<0.001). * QOL significantly improved with oral treatment (p<0.001); within 21 days of OxyContin treatment; mean pain impact scores for sleep quality, appetite, walking capacity, self- care, daily activities, mood and concentration decreased by 1.74 to   3.74 points.   * No deaths or discontinuations occurred. * No additional safety results provided. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Wang W, OuYang X, Yu Z, Chen Z. Clinical application of OxyContin hydrochloride controlled release tablets in treatment of pain suffered from advanced cancer. *Chin Ger J Clin Oncol*. 2012;  11:419-421. | OxyContin twice daily, variable | N=68 | ≥15 days | * Males and females with moderate to severe pain associated with terminal cancer (phase IV according to TNM classification) | Exclusions not reported | Single-center | * Pain remission degree (0=pain was not relieved; 4=complete remission of pain) * Pain relief rate (percentage of patients whose pain was relieved by ≥2 degrees) * QOL score based on the following parameters: appetite, sleep, daily life, mental status, and interpersonal intercourse * AEs | * Initial daily dose of OxyContin: n=45, ≤30 mg; n=12, 31-60 mg; n=11, 61-120 mg * Final titrated daily dose of OxyContin: n=30, ≤30 mg; n=16, 31-60 mg; n=18, 61-120 mg; n=4,   ≥120 mg   * Moderate cancer pain (n=18): n=18, at least moderate pain remission; n=12, complete pain remission by day 15 * Severe cancer pain (n=50): n=47, moderate pain remission; n=15 complete remission; n=28 patients reported obvious pain relief by day 15 * QOL score: Appetite, sleep, daily life, mental status, and interpersonal intercourse significantly improved compared to baseline with OxyContin (p<0.01). * AEs: constipation, nausea, vomiting, dizziness, and dysuria; psychological dependence, serious AEs, and drug abuse were reportedly not observed. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study.  *Clin Drug Investig*. 2010;30(8):489-  505. | TER 100-250  mg twice daily  CRO 20-50  mg twice daily Placebo | N=1030  ITT: N=1023 (n=344,  Tapentadol ER; n=342,  oxycodone CR; n=337) | Titration 3 weeks  Maintenace 12 weeks | Age, ≥40 years   * Diagnosis of OA of the knee * Function capacity class I-III * Pain at joint requiring use of analgesics (non- opioid/opioid dose ≤160 mg oral morphine) for   ≥3 months before screening   * Average baseline pain intensity ≥5 on 11-point NRS during 3 days prior to random- ization | * Clinical significant/ unstable medical or psychiatric disease * Requirement of painful procedure (eg, surgery) during the study * Conditions affecting OA pain assessment * Use of neuroleptics, TCAs, anticonvulsants, anti-parkinsonian drugs, SNRIs, MAOIs within 14 days of screening * Use of corticosteroids within 4 weeks to 6 months of screening * History of: substance abuse; epilepsy/seizure; stroke/transient ischemic attack; malignancy (past 2 years); HIV; chronic hepatitis B/C; uncontrolled hypertension; severe renal impairment (CrCl<60 mL/min); moderate or severe hepatic impairment; ALT/AST >3x upper limit of normal; hypersensitivity to study medications/ excipients | Randomized, Double-blind, Active- and Placebo- controlled, Parallel-arm, Multicenter, Phase III | Primary:   * In US: change in average pain intensity from baseline to week 12 of maintenance period based on NRS * In Europe: change from baseline in average pain intensity over the entire 12- week maintenance period per NRS   Safety:   * AEs including TEAEs * Patient Assessment of Constipation Symptoms (PAC-SYM) rated at baseline and end of study * Clinical Opiate Withdrawal Scale (COWS) rated at follow- up * Subjective Opiate Withdrawal Scale (SOWS) rated at follow- up | * Mean total daily dose: TER: 299.3 (107.16) mg; CRO: 48.2 (23.94) mg * Significant pain relief with TER vs. placebo (LSM difference vs. placebo at week 12: -0.7 [95% CI: - 1.04, -0.33]; LSM difference vs. placebo over 12-week maintenance: -0.7 [95% CI: -1.00, - 0.33]) * Significant pain relief with CRO vs. placebo over 12-week maintenance period but not at week 12 (LSM difference vs. placebo over 12- week maintenance: -0.3 [95% CI: - 0.67, 0.00]) * TEAEs: 61%, placebo vs. 76%, TER vs. 87%, CRO; most common TEAEs (≥10%): nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue, pruritus * TEAEs leading to D/C: 6.5%, placebo vs. 19%, TER vs. 43%, CRO; * Serious AEs: n=20 (6, placebo vs. 4, TER vs.10, CRO) * 1 death (MI, 90 days after last dose of CRO); deemed unrelated to study medication * PAC-SYM, overall score: LSM change from baseline significantly lower in TER vs. CRO (p<.001) * COWS: patients evaluated had no, mild, or moderate opioid withdrawal * SOWS: no significant difference in LSM total scores |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis- related pain: placebo- controlled trial and long-term evaluation. *Arch Intern Med.* 2000;  160(6): 853-860. | Double-blind: Fixed-dose OxyContin10 mg q12h or 20 mg q12h  Placebo q12h | N=133  OxyContin 10 mg, n=44  OxyContin 20 mg, n=44  Placebo, n=45 | 14 days | * Age ≥18 yrs * Confirmed diagnosis of osteoarthritis * Experiencing frequent or persistent pain for at least one month * Current daily pain intensity moderate or greater | * Severe organ dysfunction * History of drug or alcohol abuse | Double-blind, Randomized, Placebo- controlled, Parallel | 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 | Double-blind:   * Compare to placebo, use of OxyContin 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). * Eighty-seven (65.4%) patients reported at least one treatment- related AE during the study; no AEs were deemed life-threatening. * Treatment-related AEs occurring in   ≥10% of patients receiving OxyContin included nausea, constipation, somnolence, vomiting, dizziness, pruritus, and headache. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis- related pain: placebo- controlled trial and long-term evaluation. *Arch Intern Med.* 2000;  160(6): 853-860.  \*Cont’d\* | Extension: OxyContin q12h, variable | N=106 | 6 month extension trial with an option of additional 12 months | * Patients who participated in placebo- controlled portion of the trial |  | Open-label Extension (up to 18 months) | Primary:   * Pain intensity   Secondary:   * Quality of sleep * Activities and Lifestyles Questionnaire * Safety (AEs) * Number of night awakenings due to pain | Extension:   * Pain was controlled below a moderate level throughout the trial, with no statistically significant trends in pain scores. * Mean dose remained stable at approximately 40 mg/day after titration. * Fifty-eight patients completed 6 months of treatment, 41 completed 12 months, and 15 completed 18 months. * Sixty patients discontinued OxyContin (n=32, due to AEs). * AEs reported by ≥10% of patients included constipation, somnolence, nausea, pruritus, nervousness, headache, Insomnia. * Thirteen hospitalizations occured, five of which deemed related to OxyContin: abdominal pain (n=2), constipation (n=1), withdrawal syndrome (n=1), confusion and fall (n=1). * One patient experienced withdrawal symptoms after running out of study medication. * AEs reported by ≥ 10% of patients during the scheduled respites were nervousness (n=9) and insomnia (n=8). A small number of participants reported some other symptoms that are consistent with acute withdrawal following abrupt cessation of OxyContin therapy. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetamin-ophen added to nonsteroidal anti- inflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol.* 1999;26(4):  862-869. | Phase I: IR oxycodone  5 mg qid  Phase II: OxyContin q12h, variable (up to  60 mg/day)  IR oxycodone- APAP  5-325 mg  tablets qid, variable (up to 60 mg/day)  Placebo | Phase I: N=167  Phase II: N=107  OxyContin, n=34  IR  oxycodone- APAP, n=37  Placebo, n=36 | 30 days | * Moderate to severe osteoarthritis pain, despite use of NSAIDs | * Patients receiving: Intra-articular steroid injections in the study joint within 6 weeks of study entry * Contraindications: Allergies to APAP, oxycodone, or other opioids * Active cancer, organ dysfunction, history of substance abuse | Phase I: Open-label Titration  Phase II: Double-blind, Randomized, Double- dummy, Parallel | Primary:   * Pain intensity   Secondary:   * Quality of sleep * Safety | Phase I:   * Following titration with IR oxycodone, mean pain intensity decreased (p=0.0001) and quality of sleep improved (p=0.0001). * Mean dose was approximately 40 mg/day.   Phase II:   * Pain intensity and quality of sleep were significantly improved in both active groups vs. placebo group (p≤0.05). * Nausea (p=0.03) and dry mouth (p=0.09) were less common with OxyContin than with IR oxycodone/APAP. |
| Markenson JA, Croft J, Zhang PG, Richards P. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial*. Clin J Pain.* 2005;21(6):  524-535. | OxyContin 10 mg q12h (up to maximum dose of 60 mg q12h)  Placebo q12h | N=107  OxyContin, n=56  Placebo, n=51 | 90 days | * Persistent moderate to severe osteo- arthritis pain, not controlled by standard therapy (NSAIDs, APAP, and/or short-acting opioids) | * Allergy to opioids * Scheduled to have surgery during the study period * Had unstable coexisting disease or active dysfunction * Had active cancer * Pregnant or nursing * Had a past or present history of substance abuse * Involved in litigation related to their pain * Had intra-articular or intramuscular steroid injections involving the joint or site under evaluation within 6 weeks prior to baseline | Double-blind, Randomized, Placebo- controlled, Parallel-group | Primary:   * BPI average pain intensity * WOMAC scores at days 30 and 60 * Number of patients who discontinued due to inadequate pain control   Secondary:   * BPI score at each visit * Acceptability of pain medication | * Average OxyContin dose from day 30 to end of the study was 57 mg per day. * Average pain intensity at stable dosing was significantly lower in OxyContin group compared to placebo (p=0.042). * WOMAC Index scores for pain (p=0.001), stiffness (p<0.001), and physical function (p<0.001), as well as the composite score (p<0.001), were significantly lower in OxyContin group than placebo group at visits 3 (day 30) and 5 (day 60). * 34 (67%) of patients in placebo group discontinued due to inadequate pain control compared with 9 (16%) in OxyContin group (p<0.001). * At the final visit, patients receiving OxyContin were more satisfied with their pain medication than patients receiving placebo (p<0.001). |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate- release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain.* 1999; 15(3):179-183. | Phase I: OxyContin 10 mg q12h  IR oxycodone 5 mg qid  Dose titrated to stable pain control  Phase II: OxyContin q12h, variable  IR oxycodone qid, variable | Phase I: n=57  Phase II: n=47 | 18-24 days | * Age ≥18 years * Moderate to severe chronic non- malignant low back pain and receiving maximally effective doses of non- opioid analgesics with or without opioids | * History of substance abuse * Litigation regarding low back pain | Phase I: Open-label titration  Phase II: Double-blind, Randomized, Double- dummy, Crossover | Primary:   * Pain intensity (0-3 CAT scale)   Secondary:   * Number of rescue doses * Number of patients successfully titrated to stable pain control * Safety | Phase I:   * Pain intensity decreased from moderate to severe to slight with both oxycodone formulations.   Phase II:   * Overall pain intensity was 1.2±0.1 with OxyContin and 1.1±0.1 with IR oxycodone. * 91% of the patients were titrated to stable pain control, with no difference between formulations in the percentage of patients achieving pain control. * Patients required 0.6 doses of supplemental analgesia per day, with no statistically significant difference between treatments. * Similar safety profiles |
| Yao P, Meng LX, Ma JM, et al.  Sustained-release oxycodone tablets for moderate to severe painful diabetic peripheral neuropathy: A multicenter, open- labeled, postmarketing clinical observation. *Pain Med*.  2012;13(1):107-  114. | OxyContin q12h, variable | N=80 | Treatment period: 6 weeks | * Mod-severe pain (average pain score over last 24 hours ≥5 on NRS due to diabetic peripheral neuropathy for >4 weeks   Age, >40 years   * Able to communicate with physicians; sign informed consent | * Treatment with long- acting opioid * Pregnant/ lactating * H/o opioid drug abuse * Severe renal impairment (CrCL<10 mL/min) * Moderate-severe hepatic impairment * Contraindication to OxyContin * H/o respiratory disorders (eg, COPD), head injury, gastrointestinal disorders (eg, paralytic ileus), severe constipation * Use of MAOI within 2 weeks * Other condition(s) that violates relevant regulations of China | Multi-center, Randomized, Open-label, Observational | Primary:   * Change in pain intensity every week during 6- week treatment per NRS score; 0, no pain; 10, most severe pain   Safety:   * AEs | * Mean daily dose of OxyContin in week 1 was 16.63±7.79 mg; mean daily dose after 2 weeks was ~20 mg * After 1 week of treatment, average pain intensity score ↓ significantly (NRS: 6.8±1.4, baseline vs. 2.8±1.6, 1 week; p<0.01); NRS pain intensity scores remained < 3 through end of treatment * AEs occurred in 38 patients (47.5%); no serious AEs * AEs included: nausea, vomiting, constipation, dizziness, dry mouth, urine retention, febrile reaction |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Gimbel JS, Richards P, Portenoy RK. Controlled- release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology.*  2003;60(6):927-  934. | OxyContin q12h, variable (up to120 mg/day)  Placebo | N=159  OxyContin, n=82  Placebo, n=77 | 6 weeks | * Stable   diabetes mellitus   * Glycosylated hemoglobin (HbA1C) level of ≤11% * Distal symmetrical poly- neuropathy documented by neurologic evaluation * Reported bilateral foot pain for more than half the day for at least three months prior to enrollment * Average pain intensity score of ≥5 on an 11- point numeric scale * Moderate pain in the absence of any opioid analgesic for three days before receiving study treatment | * Impairment in swallowing or gastrointestinal function * Inability to maintain diabetic control * Receiving an analgesic regimen involving a long- acting opioid analgesic * Receiving an analgesic regimen with an average of 3 doses of a short- acting opioid per day * Patients allergic to oxycodone or other opioids * History of alcohol or substance abuse * Took any investigational drug in 30 days prior * Pregnant or lactating * Clinical indication of autonomic neuropathy | Multicenter, Double-blind, Randomized, Placebo- controlled, Parallel group | Primary:   * Average daily pain intensity over the last 24 hrs from day 28 to day 42 or discontinuation   Secondary:   * BPI   SF-36   * Rand Mental Health Inventory * Subject daily dairy for pain right now, worst pain, satisfaction with medication, and sleep quality * Sickness Impact Profile * Safety | * OxyContin was significantly more effective than placebo in the ITT population for the primary efficacy variable, overall average daily pain intensity from days 28 to 42, where the least squares mean score was 4.10.3 for the OxyContin group and 5.30.3 for the placebo group on a scale from 0 (“none”) to 10 (“pain as bad as you can imagine”) (p=0.002). * Analyses of the secondary efficacy variables overall scores for average pain intensity from days 1 to 27, pain right now, worst pain, satisfaction with study drug, and sleep quality from days 1 to 42 were also statistically improved for the OxyContin group (p<0.02). * The incidence of adverse events was greater in the OxyContin group than in the placebo group. The most commonly reported adverse events (10%) in the OxyContin group were those usually associated with opioid use: constipation, somnolence, nausea, dizziness, pruritus, vomiting, dry mouth, and asthenia. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Watson CPN, Moulin D, Watt- Watson J, Gordon A, Eisenhoffer J. Controlled- release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain.* 2003;105(1-2):71-  78. | OxyContin q12h (titrated to a maximum of OxyContin 40 mg q12h)  Active placebo (benztropine) q12h (titrated to a maximum of 1 mg q12h ) | N=36  (evaluable population) | 4 weeks per treatment for the initial study then optional open-label CR  treatment for up to one year | * Diabetes mellitus with stable glycemic control * Painful symmetrical distal sensory neuropathy * At least mod- erate pain in the lower extremities assessed at the screening visit * A medical history of moderate daily pain based on the patient’s recall over the previous three months * One or more symptoms of diabetic neuropathy * Signs of reduced sensation, strength or tendon reflexes not   attributable to any other cause | * Intolerance to oxycodone * History of drug or alcohol abuse * Significant pain of alternate etiology | Randomized, Double-blind, Crossover | Primary Measures of Efficacy:   * Daily pain intensity measured by VAS (0=no pain, 100= unbearable pain) and categorical scale (0=no pain, 4= unbearable pain). * Weekly VAS and categorical scores for steady, brief, and skin pain intensity   Primary Measure of Disability:   * PDI   Secondary:   * Pain relief (CAT, 0=complete relief; 5=pain worse)   SF-36   * Pain and Sleep Questionnaire * Treatment Preference and Satisfaction * Safety | * Compared to placebo, OxyContin resulted in significantly lower VAS (21.820.7, OxyContin vs. 48.626.6, placebo; p=0.0001), categorical pain scores (1.20.8, OxyContin vs. 2.00.8, placebo; p=0.0001), and better pain relief (1.71.3, OxyContin vs. 2.81.1, placebo; p0.0005), during the last week of treatment assessed in patients’ pain diaries. * Steady, brief, and skin pain intensities were significantly reduced with OxyContin compared to placebo (p=0.0001 for all measures). * The overall pain and sleep scores were significantly better for OxyContin compared to placebo (p=0.0003). * All variables in the PDI were significantly better with OxyContin (p0.05), with the exception of sexual behavior. * For the SF-36, OxyContin was significantly better than placebo in most health-related QOL domains. * OxyContin was preferred by 88% (p=0.0001) of patients and 80% of the cases by the investigator (p=0.0001). OxyContin was rated as moderately or highly effective by 95% of patients completing the study. * AEs were similar between treatment groups. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia.  *Neurology.*  1998;50(6):  1837-1841. | OxyContin: initial dose 10 mg q12h, increased weekly up to a maximum dose of 30 mg q12h.  Placebo | N=50  (n=38,  analysis of efficacy) | 4 weeks per treatment | * Post-herpetic neuralgia ≥3 months * Pain of at least moderate intensity for at least half a day | * Hypersensitivity to opioids * Intolerance to oxycodone * History of drug or alcohol abuse * Significant pain of alternate etiology | Double-blind, Randomized, Crossover | Primary Measures of Efficacy:   * Overall pain intensity measured by 100 mm VAS; categorical scale (0=no pain, 4=unbearable pain) * Pain relief measured by categorical scale (0=pain worse, 6=complete relief)   Primary Measure of Disability:   * Categorical scale (0=no disability, 3=severe disability)   Secondary:   * Profile of Mood Status Questionnaire * BDI * Safety * Treatment effectiveness (rated by patient) | * Patients receiving OxyContin reported lower mean daily pain intensity scores than placebo on both VAS and CAT scales (both p=0.001), and greater pain relief (p=0.001), except at Week 1. * Similar differences between treatment groups were also seen with weekly pain intensity and pain relief scores. * OxyContin group also showed significantly better scores than placebo for global effectiveness (p=0.0001), disability (0.041), and patient preference (p=0.001). |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Zhou B, Wang J, Yan Z, Shi P, Kan  Z. Liver cancer: effects, safety, and cost- effectiveness of controlled-release oxycodone for pain control after TACE. *Radiology*. 2012 Mar; 262(3):1014-21. | Three groups:   1. 20 mg CRO 1 hour before TACE (T0) and 12 (T12) and 24 (T24) hours   after T0;   1. 10 mg CRO, given at   the same intervals as group 1;   1. placebo of 100 mg vitamin C, given at the   same intervals as group 1 | N= 210  Group 1, n=70  Group 2, n=70  Group 3, n=70 | 3 days | * Patients with confirmed diagnosis of liver cancer * Number of tumors < 3 * Tumor   diameter >3 cm and <8cm | * American Society of Anesthesiologist physical status >3 * Known allergy or intolerance to CRO * Pregnancy * History of drug abuse * Long-term opioid use * Post-operative nausea, vomiting, or ileus * Liver enzyme elevation greater than three times the reference range | Prospective, Randomized, Double-blind, Placebo- controlled | * Mean highest pain intensity score via 11- point NRS (0- 3=mild, 4- 6=moderate, 7- 10=severe) at specified time periods (T0-12, T12-24, and T24-48) * QOL factors rated T0 and T48 using a 5-point categorical scale (1=worst, 2=bad, 3=mild, 4=normal, 5=very good). * AEs * Cost-   effectiveness (mean analgesic cost and hospital stay) | * The mean highest pain scores in groups 1 and 2 were significantly lower compared to group 3 for each time period (p<0.001). * The mean highest pain score in group 1 was significantly lower compared to group 2 during T0-12 (3.8±1.6 vs. 5.0±1.8; p<0.001). * Recovery of quality of sleep, appetite, spirit, and fatigue were significantly better in groups 1 and 2 than in group 3 (p<0.001) when comparing T0 and T48; appetite recovery was also significantly better in group 1 compared to group 2 (p=0.001). * AEs included nausea, vomiting, dizziness, constipation, dysuria, hypersomnia, and pruritus; no significant differences in AEs were observed. * Analgesic cost and hospital stay in groups 1 and 2 was significantly less than in group 3 (median analgesic cost, Chinese Yuan: 37.0, group 1 vs. 19.6, group 2 vs. 43.4, group 3 [p=0.002]; mean hospital stay, days: 4.2±0.4, group 1 vs. 4.3±0.4, group 2 vs. 5.1±1.1, group 3 [p<0.001]); cost was significantly lower in group 2 than in group 1 (p=0.001). |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Rothwell MP, Pearson D, Hunter JD, et al. Oral oxycodone offers equivalent analgesia to intravenous patient-controlled analgesia after total hip replacement: a randomized, single-centre, non-blinded, non- inferiority study. *Br J Anaesth*.  2011;106(6):865-  872. | Following successful spinal block, patients were randomized: OxyContin 20 mg q12h for three days (IR oxycodone for breakthrough pain)   * IVPCA with morphine 1 mg   bolus, 5 min lockout time, and no loading dose   * Both groups received non-   opioid co- analgesia and antiemetics | N=110  OxyContin, n=55  IVPCA, n=55 | 3 days | Age, 60-85 years   * ASA health status class I- III * Undergoing total hip replacement * Willing to undergo spinal anaesthesia | * Weight <45 kg, * Long-term strong opioid therapy before operation * Abnormal perioperative mental status * Inability to operate an IVPCA device * Known allergy to oxycodone or morphine | Randomized, Single-center, Non-blinded, Non-inferiority | Primary:   * Postoperative pain at rest and movement measured every 4 hours via NRS (0-10) * Nausea score recorded every 12 hours using a 0-4 scale   Secondary:   * Time to first mobilization * Total amount of opioid consumed * Number of additional antiemetic doses * Time to analgesic discontinuation | * No statistically significant differences in the primary outcome measures of pain at rest and movement (p>0.05, 95% CI: -0.41,   +0.96) or nausea scores (p>0.05) during any time period between the two treatment groups   * No significant difference between OxyContin and IVPCA in the mean total amount of opioid consumed (102 mg vs. 63 mg, respectively; p=0.053) and time to mobilization (24.45 h vs. 26.6 h, respectively; p=0.204). * The number of antiemetic doses required in the first 24 hours was significantly lower in patients treated with OxyContin compared to IVPCA (1.1 vs. 1.4, respectively; p<0.03). * The time to analgesic discontinuation was significantly shorter in the OxyContin group (50.5 h, OxyContin vs. 56.6 h, IVPCA; p<0.042). * No instances of significant respiratory depression in either group; no additional safety information was provided. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Kampe S, Wolter K, Warm M, Dagtekin O, Shaheen S, Landwehr S. Clinical equivalence of controlled-release oxycodone 20 mg and controlled- release tramadol 200 mg after surgery for breast cancer.  *Pharmacology*. 2009;84(5):276-  281. | CRO 20 mg  (1 dose at 30 min prior to surgery and 1  dose 12 h later)  CR tramadol, 200 mg (1  dose at 30 min prior to surgery and 1  dose 12 h later)  All patients received premedicatio n with 7.5 mg midazolam thirty minutes prior to surgery.  All patients had access to rescue medication post-surgery (1 gram IV paracetamol). | N=54 CRO, n=27  CR tramadol, n=27 | 24 h | * Female; Age, 18-80 years * Schedule for surgery for breast cancer * ASA physical status I-III * Weight, 40- 100 kg | * Known contraindications to oxycodone, tramadol, or paracetamol * Communication difficulties * Psychiatric disease * Pregnancy * History of alcoholism, drug abuse, chronic pain, or sleep apnea syndrome | Randomized, Double-blind | Primary   * Clinical equivalence: differences between the mean values for pain scores at rest and on coughing 8-24 hours after operation (VAS, 0 to 100); equivalence margin of ±10 on the VAS | * Mean pain scores at rest 24 h post- surgery were similar between CRO and CR tramadol (5.4 [5.82] vs. 7.4 [8.59], respectively). * The 90% CI of the mean differences between the treatment groups over 24 hours after operation at rest was within the predefined equivalence margin (90% CI: -4.5 to +1.7). * CRO and CR tramadol were equivalent in regards to mean pain scores on coughing 24 h post- surgery (6.2 [5.71] vs. 11.5 [1.43]; 90% CI: -6.2 to +1.7). * Cumulative paracetamol given over the 24-hour observation period did not differ significantly between the oxycodone group and tramadol group (1.32±.9 g vs. 1.61±1.1 g; p=0.32). * No significant differences between the treatment groups regarding adverse events, including nausea (p=0.13), vomiting (p=0.24), itching (p=0.77), sedation (p=0.97), and dizziness (p=0.35). * No significant differences were found concerning patient satisfaction scores (p=0.8) or patients' general perception of postoperative pain management (p=0.71). |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Illgen RL, Pellino TA, Gordon DB, Butts S, Heiner JP. Prospective analysis of a novel long-acting oral opioid analgesic regimen for pain control after total hip and knee arthroplasty*. J Arthroplasty.*  2006;21(6):814-  820. | Preinterventio n  Group: IVPCA either with morphine sulfate 1 to 2 mg or hydro- morphone 0.2 to 0.4 mg with a 6-minute lockout for post- operativepain management between March 2001  and June 2003  Post- intervention Group: OxyContin 20mg starting pre-operatively the morning of surgery and continued twice daily through postoperative day3 (6 doses total) and oxycodone 5 to 20 mg every 3 hours as needed between July and October 2003 | N=124  Preinter- vention group, n=62  Postinter- vention group, n=62 | 3 days | * Postoperative THA and TKA pain patients | Exclusions not reported | Prospective, pre- intervention and post- intervention design | * Visual analog pain scores * Total opioid consumption * Functional interference measures * Rates of opioid-related side effects | * No difference in the amount of moderate to severe pain in either group * OxyContin group used significantly less opioid (mean parenteral morphine equivalent) in the first 24 hours after surgery than IVPCA group (37.80±23.45 mg vs. 59.41±37.00 mg, respectively, p<0.001). * OxyContin group reported significantly less interference from pain in walking (p=0.024) and coughing (p=0.022) on day 1, falling asleep (p=0.001), staying asleep (p=0.013), coughing (p=0.004), and deep breathing (p=0.011) on day 2, and getting out of bed (p=0.05), walking (p=0.038), staying asleep (p=0.001), coughing (p=0.003), and deep breathing (p=0.003) on day 3. * No statistically significant differences in side effects were reported; on all 3 days, drowsiness was most frequently reported, followed by nausea, dizziness, and itching. By day 3, constipation became a frequently reported side effect. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| de Beer J , Winemaker MJ, Donnelly GAE , et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. *Can J Surg.*  2005;48(4):277-  83. | First 48 hours post- operatively, patients received IVPCA  (morphine) or epidural administration of a combination of morphine, fentanyl and bupivacaine.  Upon D/C, patients received –  Phase I: OxyContin 10  mg, 20 mg, 40 mg tablets q12h  Rescue medication morphine 7.5- 10 mg IM q3- 4h and APAP 325-650 mg  q4h prn  Phase II: standard analgesics according to physicians orders (ST) | N=171  Phase I: n=70 (evaluable population)  Phase II: n=101  (evaluable population) | 3 weeks | * Schedule to undergo elective primary unilateral total knee or hip replacement secondary to osteoarthritis * Able to comply with study protocol * Able to complete study diaries. | * Allergy to any opioid * A history of drug abuse * Ingestion of opioid analgesics within 24 hours before the operation * Recipient of workers’ compensation benefits * Inflammatory arthritis or significant pain of other origin | Randomized, Open-label, Parallel group studies –  Two separate 3-week studies:  Phase I: Patients enrolled Sept. 1999 to Jan.  2000  Phase II: Patients enrolled Jan. 2001 to Sept.  2001 | * Pain intensity 100-mm VAS ( 0=no pain; 100=excruciati ng pain) * 2 weeks postop BPI short (0-10 scale: 0=no pain or difficulty. 10=maximum pain or difficulty) * Pain relief * Pain intensity (composite pain score) * Functional impairment (composite functional ability score) * Length of hospital stay * Opioid   analgesic dose   * Number of opioid administrations * Adverse events coded (COSTART IV) | * At the time of discharge from hospital, patients in OxyContin group recorded lower mean (and standard deviation) pain intensity scores than the ST group (20.2 [17.9] vs. 27.7 [21.5] mm on 100- mm VAS (p=0.021). * Length of hospital stay for OxyContin group was 5.5 days compared to 6.4 days with ST (p=0.001). * Summary of BPI at 2 weeks postop found pain equally well controlled between phases, although patients displayed less function impairment in Phase I. * OxyContin patients used less opioid (morphine equivalents) while in hospital than ST patients (p<0.001). * Average number of daily administrations of analgesic in hospital for OxyContin patients was   2.1 and for the ST group 3.5 (p<0.001).   * ST group reported more nausea, vomiting, pruritus and fever than OxyContin group * OxyContin group reported more somnolence, constipation, dizziness, confusion, and tachycardia than ST group. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Wirz S, Wartenberg H, Wittmann M, Nadstawek J. Post-operative pain therapy with controlled-release oxycodone or controlled release tramadol following orthopedic surgery: A prospective, randomized, double-blind investigation. *The Pain Clinic*.  2005;17(4):367-  376. | CRO  CR tramadol | N=57 CRO, n=26  CR tramadol, n=31 | 3 days | Age, 18-65 years   * Scheduled for orthopedic surgery of the lower extremities | * Known or suspected cardiovascular, pulmonary, renal, neurological, psychiatric or allergic diseases * Lactation or pregnancy * Drug dependency * Alcoholism * Opioid tolerance * History of abuse or history of treatment with any opioids * Current treatment with analgesics other than the study medications | Prospective, Randomized, Double-blind | * Dosage * Vital Signs * Pain at rest and exercise via NRS (0=no pain, 100=worst pain imaginable) * AEs | * Mean daily doses: 21.03 mg, CRO and 211.83 mg, CR tramadol * There were no significant differences in pain at rest and during exercise over days 1-3 between the two groups. * When comparing pain levels on day 1 vs. day 3, both treatments were associated with significant decreases in pain at rest as noted at 7AM, 2PM, 7PM, and 10PM (p=0.001 for all time points, CRO; p=0.021/0.001/0.001/0.001, CR tramadol). * Pain during exercise did not significantly differ on day 1 vs. day 3 with either treatment. * No difference in the amount of rescue medication used in either treatment group. * No AEs were deemed severe by investigators; nausea was more severe with CR tramadol compared to CRO (NRS=15, CR tramadol vs. NRS=6, CRO; p=0.011). * Emesis and nightmares were reported only with CR tramadol. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Ginsberg B, Sinatra RS, Adler LJ, et al.  Conversion to oral controlled-release oxycodone from intravenous opioid analgesic in the postoperative setting. *Pain Medicine.*  2003;4(1):31-38. | Patients converted to OxyContin q12h from IVPCA opioid (usually morphine) at least 12 hours post- procedure | N=189 | 7 days | * Hospitalized patients (aged 18-70 years) recovering from elective major surgery (abdominal, orthopedic, gynecologic, or urologic) who had been treated post- operatively with IV opioid analgesics for at least 12 hours after surgery, either by continuous infusion or IVPCA * Patients anticipated to require opioid analgesia for more than a few days were enrolled when they could tolerate oral medications | * Patients with evidence of paralytic ileus, nausea and vomiting, significant respiratory depression, or other known contraindications to opioid therapy were excluded | Multicenter, open-label, usual-use | Primary:   * Average conversion factors * Average daily dose of OxyContin * Pain Intensity (NRS, 0-10)   Secondary:   * Comfort level scale (0-10) * Quality of sleep scale (0-10) * Patient acceptance scale (0-10) * Safety | * Mean conversion factors for patients converting from IV morphine to OxyContin for the various types of surgery ranged from 1.2 to 1.3, with the overall average being 1.2 (±0.1 SE). * At 6 hours after the initial dose of OxyContin, patients reported significantly (p<0.001) lower pain intensities than with IVPCA for all patients combined (average pain scores for all patients combined were 4.10.2 SE at baseline and 3.30.2 SE at 6 hours after the initial dose of OxyContin) * Adequate and effective pain control (defined for this study as pain intensity scores 4) was maintained with OxyContin over the duration of the study * One-third of patients required around-the-clock OxyContin therapy for at least 7 days, with the mean daily dosage declining from 563 mg on the 1st day to 273 mg on the 7th day. * The most commonly reported (≥10%) AE were constipation, nausea, and pruritus, and were also the most common adverse events leading to dose reduction or premature discontinuation. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Cheville A, Chen A, Oster G, et al. A randomized trial of controlled- release oxycodone during inpatient rehabilitation following unilateral total knee arthroplasty, *J Bone Joint Surg.* 2001;83- A(4):572-576. | OxyContin 20 mg qAM and 10 mg qPM titrated up to max of OxyContin 30 mg q12h.  Placebo  Rescue analgesia: IR oxycodone 5 mg prn q4h | Screened: N=135  Randomized: N=59  OxyContin, n=29  Placebo, n=30 | 15 days | * Patients admitted for inpatient rehabilitation within 7 days following unilateral TKA performed for the treatment of OA or RA * Moderate to severe pain and cleared to bear weight fully on the involved extremity at the time of admission * English speaking | * History of drug abuse or evidence of cognitive impairment | Double-blind, Randomized, Parallel | * Discharge time * Pain intensity * Functional Independence Measures * Physical performance * Range of knee motion * Knee extensor torque * Safe ambulation velocity * Opioid side- effects | * Compared to placebo, OxyContin group reported significantly less pain and significantly greater ROM (passive motion, p=0.036; active motion, p<0.001) and quadriceps strength (p=0.001) by the eighth (final) physical therapy session. * OxyContin group was also discharged from the hospital at an average of 2.3 days earlier than the patients in the placebo group (p=0.013). * The OxyContin treated group requested significantly less rescue medication (p=0.02). * No difference in opioid-related side effects between gropus was reported; specific side effects were not reported by authors. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled- release oxycodone for noncancer pain: results of a 3-year registry study.  *Clin J Pain*. 2007; 23(4): 287-299. | OxyContin q12h | N=219 (ITT) | 3 years | * Previously participated in one of five chronic noncancer pain OxyContin studies * Age ≥18 years * Persistent back pain, OA pain, and painful diabetic poly- neuropathy, and continued to require analgesia for the management of their moderate to severe pain * Physician approved of the patient’s participation in the registry * Able to sign written informed consent * Able to swallow tablets whole | * Pregnant or had the potential to become pregnant * Were truly allergic to oxycodone or had a history of allergy to other opioids * Had active cancer with ongoing chemotherapy or radiotherapy * Known past or present history of substance abuse or alcohol abuse * History of or active severe organ dysfunction or a physical or psychological disease which may put them in increased risk with the study medication * Had been or were currently involved in any litigation that was related to the patient’s pain and/or injury | 3-year, Multi- center, Open- label, Usual use Registry study | * Patient Acceptability of Pain Medication (1=not acceptable, 6=totally acceptable) * Average Pain Intensity [BPI: 0=no pain, 10=pain as bad as you can imagine] * Patient Satisfaction with Medication (0=not at all satisfied, 10=totally satisfied) * Patient Generated Index Score (PGI: 0=the worst you can imagine, 100=exactly as you would like it to be) * Safety (AEs) | * Mean duration of OxyContin use was 541.4370 days * Mean daily dose over the course of the study was 52.538.5 mg (range of 10 to 293.5 mg); after the initial titration, the mean dose of study medication remained relatively stable throughout the study. * BPI average pain intensity scores declined after treatment with OxyContin (5.1±2.2, baseline vs. 4.4±2.1, end of month 3). * At the end of month 3, 52% of patients rated their average pain intensity from 0 to 4 (“mild” on BPI), and after month 3, 56% of the patients never had an increase in pain >2 points. * Patient acceptability of pain medication scores increased from baseline to month 3 and remained elevated for the duration of the study (p0.05 through month 27). * The observed patient satisfaction with medication scores improved and remained higher than baseline through month 33 (p0.05 through month 33). * Observed mean changes in PGI scores increased from month 3 to 24 and then stabilized, indicating increases in patients’ satisfaction with the activities they chose at baseline as ones that were important for them to improve (p0.05 through month 24). * Constipation (15%) and nausea (12%) were the most frequently reported treatment-related AEs. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Binsfeld H, Szczepanski L, Waechter S, Richarz U, Sabatowski R. A randomized study to demonstrate noninferiority of once-daily OROS hydromorphone with twice-daily sustained release oxycodone for moderate to severe chronic noncancer pain. *Pain Pract*.  2010;10:404-415.  Richarz U, Waechter S, Sabatowski R, Szczepanski L, Binsfeld H. Sustained safety and efficacy of once-daily hydromorphone extended-release (OROS®  hydromorphone ER) compared with twice-daily oxycodone controlled-release over 52 weeks in patients with moderate to severe chronic noncancer pain. *Pain Pract*. 2013 Jan;13(1):30-40. | Twice daily CRO, variable  Once daily ERH, variable | Core phase: N=277  Extension phase: N=112 (ERH, n=60; CRO, n=52) | Core phase: weeks 0-24  Extension phase: weeks 24  through 52 | Age, ≥18 years   * Chronic noncancer pain, defined as pain occurring ≥20 days/month for >3 months * Continuous opioid therapy required | * Previous unsuccessfull therapy with hydromorphone or oxycodone therapy * Known hypersensitivity to either drug * History of significant cardiac, nervous system, or gastrointestinal conditions, moderate-to severe hepatic impairment, severe renal impairment, or hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose- galactose malabsorption * Pregnant or breastfeeding | International, Multicenter, Open-label, Randomized, Parallel group, study with a 28- week extension phase (core phase: weeks 0-24;  extension phase: weeks 24 through  52) | Primary:   * Change in BPI pain severity item (“pain right now”) score from baseline to week 38 and week 52 (NRS, 0-10).   Secondary:   * BPI items, “pain at its worst”, “pain relief”,   and individual pain- interference items.   * Global assessment of efficacy and convenience of the study drug assessed at week 52. * Sleep assessment at weeks 38 and 52 via BPI sleep interference item, Medical Outcomes Study scores, and Short-Form 36 (SF-36)   Safety:   * AEs * Global assessment of tolerability | * Mean duration of exposure: 371.0 days, ERH vs. 380.5 days, CRO * Mean ERH dose: 16.1 mg/day at week 4; 17.1 mg/day at week 52 * Mean CRO dose:40.4 mg/day at week 4; 44.6 mg/day at week 52 * Mean change in “pain right now” from baseline to week 38 was -3.0 (0.3) for ERH compared to -2.8 (0.3) for CRO; remained similar through week 52 (-2.9 [0.3] vs. -2.8 [0.3]. * Mean “pain at its worst”, “pain at its least”, pain interference scores, SF- 36 scores, and sleep quality improved from baseline to week 52 with ERH and CRO. * Patient-rated global assessment: 91.7% of ERH patients and 86.5% of CRO patients rating efficacy as “very good/good”. * AEs were reported by 85 patients (n=42, ERH and n= 43, CRO). * Most common AEs (>5% of patients) included weight decrease, anorexia, hypertension with ERH and nasopharyngitis, vertigo, and drug withdrawal syndrome with CRO. Majority of the AEs were regarded as mild to moderate in severity. * Serious AEs: n=6, ERH vs. n=4, CRO. * No deaths reportedly occurred during the study. * Discontinuation of therapy: N=15; n=5 discontinued due to AEs. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Gatti A, Longo G, Sabato E, Sabato AF. Long-term controlled-release oxycodone and pregabalin in the treatment of noncancer pain: an observational study. *Eur Neurol*. 2011;65(6):317-  322. | OxyContin and pregabalin, variable | N=1,015 | 1 year | Age, ≥18 years   * Chronic noncancer pain, defined as a score of   >5 on an 11- point NRS (0=no pain, 10=worst pain imaginable) for ≥6 months   * Failed to respond to other analgesic therapies | Exclusions not reported | Single-center, Open-label, Prospective Cohort | * Pain intensity over the last 24 hours at scheduled study visits (months 1, 2, 4, 6, 9, and 12) via11-point NRS * AEs * Onset of addiction | * OxyContin mean starting dose: 12.5±8.4 mg/day (range, 10-100 mg/day) * Pregabalin starting dose: 121.7±97.2 mg/day (range, 50-600 mg/day). * Initial increase in dose during the first 4 months of the study for OxyContin and first 6 months for pregabalin; doses of both drugs gradually reduced over the remainder of study. * Mean NRS scores significantly decreased (7.02±1.26, baseline vs. 1.45±0.92, 12 months; p=0.00001), and improvements were observed between consecutive visits (p<0.001). * Majority of AEs were deemed mild to moderate in severity; AEs included nausea, constipation, somnolence, and edema. * Frequency of nausea and somnolence decreased significantly between all consecutive visits (p<0.05) * Three patients (all >65 years of age) affected by serious diseases died during the study * Study discontinuations: n=234 (n=159, AE-related; n=59, complete pain relief at 4 months); rate of discontinuation significantly decreased at month 2 vs. month 1 (p=0.033) * AEs resulting in discontinuation in   ≥5% of patients: constipation, somnolence, nausea (13.8%), dizziness, vomiting, mental confusion, and edema.   * No cases of addiction were reportedly identified. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Giuggioli D, Manfredi A, Colaci M, Ferri C. Oxycodone in the long-term treatment of chronic pain related to scleroderma skin ulcers. *Pain Med*. 2010;11(10):1500  -1503. | OxyContin q12h, variable  All patients continued systemic (calcium- channel blockers and/or prostanoids) and local (surgical debridement and moist dressing) standard therapies for the management of scleroderma skin ulcers | N=29 | Follow-up: baseline, 1 month, end of therapy | * Met the American College of Rheumatology classification criteria for Systemic Sclerosis * Severe pain (categorized per World Health Organization guidelines) due to skin ulcers * Severe pain uncontrolled by maximum doses of both NSAIDs and tramadol. | Exclusions not reported | Single-center, Open-label | * Patient-rating pain per VAS * Number of hours of sleep per night and Quality Index (PSQI) questionnaire * Health Assessment Questionnaire- Disability Index (HAQ-DI) * Use of other analgesics * AEs, vital signs and laboratory parameters | * Mean dose range: 20-40 mg/day * Mean duration of treatment: 7.9±3.2 months * After one month of OxyContin treatment, VAS pain scores significantly decreased from 93.8±8.72 to 56.7±10.4 (p<0.0001); further improved to 42.9±14.9 after 3 months and remained stable through the remainder of the study * Total number of hours of sleep significantly improved after 1 month of therapy (3.68±1.28 hours, baseline vs. 5.27±0.75 hours, month 1; p<0.0001) and continued to improve through month 3 (6.10±0.95 hours). * PSQI significantly decreased from 9.72±3.95 to 3.37±1.04 after 1 month of OxyContin therapy(p<0.0001); remained stable through 3 months * HAQ-DI scores decreased from 1.1±0.67 at baseline to 0.46±0.46 at last evaluation. * N=8 required supplemental analgesia at month 3 of OxyContin therapy compare to 11 patients after 1 month of therapy * No severe AEs or changes in physical examination or laboratory parameters were observed * Constipation after 1 month of OxyContin treatment was reported by 15 patients (51.7%); n=9 (31%) reported itch, nausea, and/or dizziness * No patient reportedly presented with abstinence phenomenon after discontinuation of OxyContin |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Wild EJ, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis  pain. *Pain Practice*. 2010;10(5):416-  427. | OxyContin twice daily (20 mg to 50 mg)  TER twice daily (100 mg  to 250 mg) | N=1,117  (OxyContin, n=223; TER, n=894)  ITT=1,095  (OxyContin, n=219; TER, n=876) | 1 year | * Adults (age,   ≥18 years)   * Moderate to severe knee or hip OA pain or low back pain of nonmalignant origin, with at least a 3- month history of pain prior to screening * Dis- satisfaction with current analgesic therapy * Pain intensity score of   ≥4 on an 11-point NRS at baseline following a 3- to 7- day washout of prior analgesic treatment | * Lifelong history of seizure disorder or epilepsy * Mild or moderate brain injury within 1 year of screening or severe traumatic brain injury within 15 years * Residual sequelae suggestive of changes in consciousness * Malignancy within 2 years of screening (except successfully treated basal cell carcinoma) * Alcohol/drug abuse * History of chronic hepatitis B/C or HIV * Allergy or contraindication to oxycodone or APAP * Surgery of back or reference joint within 3 months of screening * Moderate to severe hapatic impairment * Severe renal impairment * Uncontrolled hypertension | Phase 3, Open-label, Randomized, Multicenter, Parallel group, Active- controlled, | Efficacy:   * Average pain intensity over the previous 24 hours (11-point NRS; 0=no pain, 10=pain as bad as you can imagine)   Safety:   * AEs * Severity of constipation symptoms per the Patient’s Assessment of Constipation Symptoms (PAC-SYM) questionnaire ( 0=“absence of symptoms” to 4=“very severe symptoms”) * Opioid withdrawal syndrome following discontinuation of treatment via Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opiate Withdrawal Scale (SOWS). | * Completers: TER, n=413 (46.2%) and OxyContin, n=78 (35%). * Study medication was taken for at least 6 months by 54.5% (n=487) of patients in the TER group and 41.1% (n=92) of patients in the OxyContin group, and for at least one year by 25.4% (n=227) of the TER group and 19.6% (n=44) the OxyContin group. * For completers, the mean (SD) total daily dose for TER was 380.5 mg (102.43) and 71 mg (22.89) for OxyContin. * In the TER group, mean (SE) pain intensity scores decreased from 7.6 (0.05) at baseline to 4.4 (0.09). In the OxyContin group, the decrease was from 7.6 (0.11) to 4.5 (0.17). * At least one treatment-emergent AE was reported by 85.7% (n=766) TER patients and 90.6% (n=202) OxyContin patients * The most common TEAEs (reported by >10% in either treatment group) included constipation, nausea, dizziness, somnolence, headache, fatigue, vomiting, and pruritus, * TEAEs were the most common reason for treatment discontinuation in both groups (22.1%, TER; 36.8%, OxyContin). * The incidence of serious TEAEs was 5.5% (n=49) in the TER group and 4% (n=9) in the OxyContin group. * There were no deaths during the study |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Nicholson B, Ross E, Sasaki J, Weil  A. Randomized trial comparing polymer-coated extended-release morphine sulfate to controlled- release oxycodone HCl in moderate to severe nonmalignant pain. *Curr Med Res Opin*. 2006;22(8):1503- 14. | CRO q12h  MSER once daily | N=112  enrolled patients (n=59, CRO  and n=53, MSER)  Safety: n=108 (n=50, CRO  and n=58, MSER)  ITT: n=97 (n=54, CRO  and n=43, MSER) | 6 months | Age, 18-  85 years   * Baseline pain score ≥4 on a VNS (0=no pain, 10=worst pain imaginable) | * Pain related to an underlying malignant condition * Hypersensitivity to morphine, oxycodone, or other opioids * Impaired bowel motility or intractable vomiting caused/agitated by opioid * Significant respiratory diseases (including asthma)/respiratory distress that was likely to be agitated by opioids * History of clinically significant or abnormal baseline laboratory abnormalities that might affect study results * Likelihood of requiring drugs not permitted by the study protocol * Any condition, which, in the investigator’s judgment, might affect study results, increase risk to patient, decrease chance of obtaining satisfactory data to achieve objectives * Any condition rendering the patient unable to understand any component of the study or evidence of uncooperative attitude * Pregnant, lactating, postmenopausal (<1 year) women or those unwilling to use a medical accepted method of contraception | Phase IV, Prospective, Multi-center, Randomized, Open-label, Blinded | * QOL via Physical (PCS) and Mental (MCS) Component Summary scores * Change in pain intensity from week 0 to weeks 2, 4, 8, 12, and 24 per 11-point VNS (0=no pain, 10=worst pain imaginable) * Change in sleep quality from week 0 to subsequent visits per 11- point VNS * Patient Global Assessment * Clinician Global Assessment * AEs including TEAEs | * CRO mean daily doses: 34.0±22.63 mg, baseline and 84.7±66.14 mg, study completion * MSER mean daily doses: 30.0±27.18 mg, baseline and 78.7±55.62 mg, study completion * CRO and MSER significantly increased PCS scores by week 24 (p<0.05); mean MCS scores significantly improved with CRO by week 24 vs. baseline (p<0.05). * Pain scores significantly decreased from baseline to week 24 with both treatments (p<0.05); no significant difference between therapies * MSER lead to a ‘clinically meaningful’ decrease in pain at week 8 and week 24 (change: -2.1 and -2.0, respectively). * CRO and MSER significantly improved sleep scores through week 24 (p<0.05). * From week 2 through week 24, both treatment groups reported significantly greater satisfaction with their study medications compared to baseline (p<0.001), * Physicians’ global assessment of therapy also improved compared to baseline (p<0.001) * N=66 patients (61%) experienced AEs (n=47, TEAE; n=12, serious AEs); * Significantly lower rate of constipation with CRO (p=0.043). * Discontinuations due to AE: N=28 (n=15, MSER and n=13, CRO) * No deaths occurred. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Bruera E, Belzile M, Pituskin E, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled- release oxycodone with controlled- release morphine in patients with cancer pain. *J Clin Oncol.*  1998;16(10):  3222-3229. | OxyContin q12h, variable  MS Contin q12h, variable | N=32 | 7 days | * Age ≥18 years * Pain due to cancer * Currently receiving opioid therapy | * Active anticancer therapy * Physical or mental inability to comply with protocol * Intolerance to oxycodone or related compounds * Impaired hepatic or renal function * Impaired ventilatory function * Use of an investigational drug * Pregnancy or lactation * Inability to take oral medications | Double-blind, Double- dummy, Randomized, Crossover | Primary:   * Pain intensity (100 mm VAS; 0-4 CAT scale).   Secondary:   * Effectiveness * Treatment preference * Safety | * There were no significant differences between treatment groups on measures of pain intensity, clinical effectiveness, and treatment preference (all p>0.05). * There was no significant difference in adverse effects. |
| Stambaugh JE, Reder RF, Stambaugh MD, et al. Double- blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate- release oral oxycodone in cancer pain patients. *J Clin Pharmacol.*  2001;41(5):  500-506. | Phase I:  IR oxycodone qid  Phase II: OxyContin q12h, variable  IR oxycodone qid, variable | N=40 | Phase I:  20-21 days  Phase II:  3-7 days | * Age ≥18 years * Moderate to severe cancer pain not requiring   ≤240 mg/day oral oxycodone equivalent   * Ability to take oral medications | * Primary tumor or metastatic disease in the brain * Receipt of chemotherapy within 3 days of study entry * Evidence of drug abuse * Severe cognitive impairment * Compromised renal and hepatic function | Phase I: Open titration period  Phase II: Double-blind, Randomized, Crossover | Primary:   * Global pain intensity   (0-10) of  OxyContin vs oxycodone IR at end of double period  Secondary:   * Acceptability of therapy (CAT, 1-5) * Pain relief * Pharmacokineti cs * Safety | Phase I:   * Mean pain intensity decreased from a baseline of 6 (2.2) to 2.7 (1.1).   Phase II:   * Pain intensity remained stable, with no significant differences between treatment groups on scores of pain intensity or acceptability of therapy (p>0.05). |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Kampe S, Warm M, Kaufmann J, et al. Clinical efficacy of controlled-release oxycodone 20mg administered on a 12-h dosing schedule on the management of postoperative pain after breast surgery for cancer. *Curr Med Res Opin.* 2004;  20(2):199-202. | OxyContin 20 mg q12h x  2 doses Placebo | N=40  OxyContin, n=20  Placebo, n=20 | 24 hours | * Women undergoing breast surgery for cancer   Age, 18-85 years   * ASA physical status I-III * Weight, 50- 90 kg * Height, 150- 190 cm | * Any contraindications to oxycodone * Alcoholism * Psychiatric disease * History of opioid dependency * Communication difficulties that would prevent reliable postoperative assessment | Prospective, Randomized, Placebo- Controlled, Double-blind | Primary:   * AUC based on opioid IVPCA consumption over 24 hours   Secondary:   * AUC over 24 hours for wound pain at rest and on movement as assessed by VAS * AUC over 24 hours of quality of pain management as measured on a 4 point scale (1=poor to 4=excellent) * Safety | * The AUC for IVPCA was significantly lower for OxyContin compare to placebo (146±100 mg x time vs. 252±147 mg x time, respectively; p=0.01). * AUC for VAS scores at rest was significantly lower for OxyContin compared to placebo (92±91 mm x time vs. 188±193 mm x time, respectively; p=0.05). * No significant difference in AUC for VAS scores on movement or AUC for overall quality of analgesia between OxyContin and placebo. * The most common adverse event in both the OxyContin and placebo groups was nausea (55% and 35%, respectively; p=0.34). * No patients demonstrated signs of confusion, agitation, respiratory depression, pruritus, arterial hypotension, hypertension, bradycardia, or tachycardia. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Drug Regimens/ Treatments** | **Sample Size (n)** | **Length of Study & Follow-Up** | **Inclusion Criteria** | **Exclusion Criteria** | **Design** | **Endpoints** | **Results/Statistical Significance** |
| Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo- controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster.  *Pain*. 2009;  142(3):209-217. | CRO  Gabapentin Placebo | N=87 CRO, n=29  Gabapentin, n=29  Placebo, n=29 | 35 days | * Patients with herpes zoster rash onset within 6 calendar days * Worst pain in the past 24 hours rated   ≥3 on a 0-10 numerical rating scale | * Prodrome of unilateral dermatomal pain in the area of the rash beginning >7 days prior to rash onset * Significant cutaneous or visceral dissemination or immunosuppression * Any clinically significant cognitive impairment * Systemic antiviral therapy within 8 weeks prior to baseline (except acyclovir, famciclovir, or valacyclovir if the subject agreed to take study famciclovir instead) * Alcohol or drug abuse history (past 5 years\* * Use of TCAs, antiepileptic medications, mexiletine, any topical analgesics, or nerve block of the affected or adjacent dermatomes within 2 weeks prior to the baseline visit and for 1 month after randomization * Use of opioid analgesics or tramadol on a regular basis within 2 weeks prior to the baseline visit and for 1 month after randomization * Inability to limit use of APAP to a max of 2500 mg/day while receiving 3rd tier rescue medication * Lactating women and women who could become pregnant | Randomized, Double-blind, Placebo- Controlled | Primary:   * Non- completion of trial   Secondary:   * Pain intensity ratings and NNT (clinically meaningful pain relief =   ≥30% pain reduction from baseline)   * BPI Interference Scale (QOL) * Rescue analgesia use * Safety, including NNH due to AE or serious AE | * Noncompletion: n=8 (27.6%), oxycodone CR vs. n=5 (17.2%), gabapentin vs. n=2 (6.9%), placebo (CRO vs. placebo, p=0.02; gabapentin vs. placebo, p=0.11). * Treatment with CRO significantly reduced the average worst pain over days 1-8 (p=0.01) and days 1- 14 (p=0.02) vs. placebo. * Results for days 1-28 were consistent with a benefit of CRO vs. placebo, but were not statistically significant (p=0.14); Gabapentin did not show greater efficacy over placebo in any observation period. * The NNT for clinically meaningful pain relief over days 1-14 was 2.9, CRO vs. 9.6, gabapentin. * The NNH for discontinuing participation due to an AE or serious AE was 5.8 for CRO vs.   9.7 for gabapentin.   * No significant change in QOL measures were reported. * There was less use of all three tiers of rescue analgesia in the CRO group compared to gabapentin and placebo groups, but was not significant . * Four subjects with serious AEs (OCR: disorientation and dehydration [n=1] and pre-syncope [n=1]; gabapentin: fever [n=1]; placebo: congestive heart failure [n=1]). * AEs with the greatest differences in incidence between CRO or gabapentin and placebo included constipation, dizziness, drowsiness, emesis, nausea, and sedation. |

AE=adverse event; APAP=acetaminophen; AUC=area under the curve; BPI=Brief Pain Inventory; BDI=Beck Depression Inventory; CAT= categorical rating scale; CI=confidence interval; CR=controlled-

release; CRO=controlled-release oxycodone; DB=double-blind; D/C=discontinuation; ER=extended-release; ERH=extended-release hydromorphone; FACT-G= Functional Assessment of Cancer Therapy– General; IM=intramuscular; IR=immediate-release; ITT=intent-to-treat; IVPCA=intravenous patient controlled analgesia; MDD=mean daily dose; MSER=morphine sulfate extended-release; NNH=number needed to harm; NNT=number needed to treat; NRS=numerical rating scale; NSAIDs=non-steroidal anti-inflammatory drugs; OA=osteoarthritis; PK/PD=pharmacokinetic/pharmacodynamic; PT=physical therapy; POMS= Profile of Mood States Questionnaire; q12h=every 12 hours; QID=four times daily; QOL=quality of life; RA=rheumatoid arthritis; ROM=range of motion; TCA=tricyclic antidepressant; TEAE=treatment-emergent adverse event; TER=tapentadol extended-release; THA=total hip arthroplasty; TKA=total knee arthroplasty; VAS=visual analog scale; VNS=visual numeric scale; WOMAC=Western Ontario and McMaster Universities Arthritis Index

## ry of Evidence from Secondary Sources

Riley J, Eisenberg E, Muller-Schwefe G, Drewes AM, Arendt-Neilsen L. Oxycodone: a review of its use in the management of pain. *Curr Med Res Opin*. 2008;24(1):175-192.

A systematic review evaluated the role of oxycodone within clinical settings to provide an evidence-based perspective on its use in the clinic. Randomized trials of controlled-release oxycodone in moderate-to-severe chronic neuropathic, somatic, or cancer pain were identified.

The efficacy of controlled-release oxycodone has been demonstrated in randomized, controlled trials in neuropathic pain, postherpetic neuralgia, diabetic neuropathy, osteoarthritis-related pain, low back pain, and postoperative pain. The side effect profile of controlled-release oxycodone is comparable to other opioids, with the most common side effects reported being constipation, sedation, and nausea.

Reid CM, Martin RM, Sterne JA, Davies AN, Hanks GW. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166(21):837-843.

A systematic review of randomized controlled trials evaluated the efficacy and tolerability of oxycodone in cancer-related pain.

All routes of drug administration and all formulations of oxycodone were considered, however, studies of combination oxycodone preparations (eg, oxycodone and acetaminophen) were excluded. Four studies, comparing controlled-release oxycodone with either controlled-release morphine (n=3) or controlled-release hydromorphone (n=1) were suitable for meta-analysis.

Standardized mean differences in pain scores comparing oxycodone with control groups were pooled using random-effects models. Overall, there was no evidence that mean pain scores differed between oxycodone and control drugs (pooled standardized mean difference, 0.04; 95% confidence interval [CI], -0.29 to 0.36; p=0.8; I2=62%). In meta-regression analyses, pain scores were higher for oxycodone compared with morphine (0.20; 95% CI, -0.04 to 0.44) and lower compared with hydromorphone (-0.36; 95% CI, -0.71 to 0.00).

The point estimates for the pooled odds ratio comparing oxycodone with control groups were 0.75 (95% CI, 0.51-1.10) for nausea and 0.72 (95% CI, 0.49-1.06) for vomiting. There was heterogeneity in estimates of the association of oxycodone with dry mouth and drowsiness (I2=74% and I2=71%, respectively). When the meta- analysis was repeated using only data from the trials with morphine as the control treatment, the pooled odds ratio favored oxycodone for dry mouth (OR, 0.56; 95% CI, 0.38-0.83) and drowsiness (OR, 0.72; 95% CI, 0.47- 1.1). Overall, the discontinuation rate due to adverse events was 13% (29/222) when data from all of the studies were combined; as many as 90% of patients experienced opioid-related adverse effects in each trial.

Discontinuation rates due to adverse events were similar in the oxycodone and control groups.

Rischitelli DG, Karbowicz SH. Safety and efficacy of controlled-release oxycodone: a systematic literature review. *Pharmacotherapy*. 2002;22(7):898-904.

A systematic review of 16 clinical trials identified in the MEDLINE database from January 1994 to October 2000 evaluated the safety and efficacy of controlled-release (CR) oxycodone.

Seven studies addressed the safety and efficacy of CR oxycodone for the treatment of noncancer pain. CR oxycodone was superior to both placebo and nonsteroidal anti-inflammatory drugs in relieving self-reported pain. However, there were no significant safety or efficacy differences when compared with immediate-release (IR) oxycodone for the treatment of noncancer pain.

Six studies compared the safety and efficacy of CR oxycodone with IR oxycodone in cancer and noncancer pain. Only one of these studies found that the controlled-release formulation was superior to the IR formulation in treating postoperative pain, with lower dosages, improved pain control, and fewer side effects. The remaining five studies showed no significant differences in analgesic effect between IR and CR oxycodone.

Differences in specific adverse effects between CR and IR oxycodone were inconsistent among trials. Adverse effects such as nausea, somnolence, dizziness, constipation, pruritus, and headache were reported in both treatment groups in all studies. In three trials, there was no statistically significant difference in adverse effects between controlled-release and immediate-release oxycodone. However, in a trial conducted in 164 patients with cancer, the frequency of headache and gastrointestinal adverse effects was lower with CR oxycodone than with IR oxycodone. In another trial conducted in 107 patients with osteoarthritis pain, nausea was reported less frequently by patients treated with CR oxycodone. Thus, half of the studies comparing IR oxycodone with the CR formulation showed no significant difference in side effects. The review suggested that IR and CR preparations of oxycodone have similar efficacy and comparable side effect profiles for the treatment of cancer and noncancer pain.

Five randomized, double-blind clinical trials compared the efficacy of CR oxycodone with other long-acting opioids. Four of them compared CR oxycodone with CR morphine and found no difference in analgesic efficacy between the two treatments. One study reported a higher frequency of itching and scratching with CR morphine than with CR oxycodone. Another study showed a similar frequency of adverse effects with the two drugs, but vomiting was associated more frequently with CR morphine while constipation was associated more frequently with CR oxycodone. No increase in any one adverse effect was noted in these four trials. In a comparison of CR oxycodone and hydromorphone, no difference in analgesic efficacy or adverse effects was observed. These five studies suggest neither an advantage in analgesic efficacy nor a consistent significant decrease in adverse effects between controlled-release formulations of oxycodone, morphine, or hydromorphone.

**4. ECONOMIC VALUE AND MODELING REPORT**

Modeling report not available.

**5. OTHER SUPPORTING EVIDENCE**

## Summarizing Other Relevant Evidence

* + 1. **lished and Unpublished Studies Supporting Labeled and Off-Label Indications**

**OxyContin Abuse Deterrence Studies**

Purdue conducted laboratory manipulation and extraction studies and clinical abuse potential studies that are

in accordance with the FDA’s 2015 Final Guidance on Abuse‐Deterrent Opioids: Evaluation and Labeling (FDA 2015). FDA has concluded that OxyContin has abuse-deterrent properties that are expected to deter misuse

and abuse via snorting and injection, resulting in abuse-deterrence labeling claims indicating that the product is formulated with physicochemical barriers to abuse and is expected to result in a meaningful reduction in abuse. However, abuse of OxyContin by the intravenous, intranasal, and oral routes is still possible. The methodology and results of these studies are summarized in section 9.2 of the OxyContin [Full Prescribing Information](http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o).

Additional data, including epidemiological data, when available, may provide further information regarding the real-world abuse liability and other real-world characteristics of OxyContin. Accordingly, section 9.2 may be updated in the future, as appropriate.

Prior to the approval of reformulated OxyContin by FDA in April 2010, a comprehensive evaluation of the tablet’s physicochemical properties and potential to deter abuse was conducted. These experiments, designed by experts in drug abuse and abuser tampering approaches, demonstrated that defeating the reformulated tablet’s controlled-release properties requires more time and effort than for original OxyContin (Cone et al.

2013).

For the purposes of describing the results of studies of the abuse-deterrent characteristics of OxyContin resulting from a change in formulation, the original formulation of OxyContin, which is no longer marketed, will be referred to as “original OxyContin” and the reformulated, currently marketed product, will be referred to as OxyContin.

*In Vitro Testing*

As stated in the OxyContin FPI, in vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OxyContin to resist crushing, breaking, extraction and dissolution in small volumes using a variety of tools and solvents. The results of these studies also support this finding for OxyContin relative to an immediate-release oxycodone. When subjected to small volumes of an aqueous environment, OxyContin gradually forms a viscous hydrogel (ie, a gelatinous mass) that resists passage through a needle (Cone et al. 2013).

A publication describing the development of a model for in vitro laboratory assessment of OxyContin with comparisons to original OxyContin has been published and is available at: <http://dx.doi.org/10.1016/j.drugalcdep.2012.12.006>(Cone et al. 2013).

*Clinical Studies*

The impact of OxyContin’s properties on abuse potential was evaluated in multiple human pharmacokinetic and clinical abuse potential studies. The results from these studies suggest that reformulated OxyContin should be less attractive as a drug of abuse when the method of abuse requires the tablet to be manipulated. These studies have been published and are available online via the following links: <http://onlinelibrary.wiley.com/doi/10.1002/jcph.235/pdf>(Harris et al. 2014) <http://rd.springer.com/article/10.1007/s40261-013-0085-x>(Perrino et al. 2013) <http://jop.sagepub.com/content/27/9/808.long>(Sellers et al. 2013).

The OxyContin FPI describes one of these clinical abuse potential studies conducted in recreational opioid users. While this particular study evaluated pharmacodynamic, pharmacokinetic, and safety measures of intranasally active and placebo drug treatments, only the pharmacodynamic outcomes are described in the OxyContin FPI. Further, although the study design included five treatment arms consisting of intranasally administered finely and coarsely crushed OxyContin tablets, finely crushed original OxyContin tablets, powdered oxycodone HCl, and placebo, data for only three of the treatment arms are described in the FPI.

This was a randomized, double-blind, placebo-controlled 5-period crossover study in recreational opioid users with a history of intranasal drug abuse. Subjects received intranasally administered finely crushed OxyContin 30 mg tablets, coarsely crushed OxyContin 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo (Harris et al. 2014)

Eligibility criteria for study enrollment included healthy male and female adults (aged 18 to 55 years) who were non-physically-dependent recreational opioid users as determined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria and confirmed by naloxone challenge.

Subjects had a history of nonmedical use of opioids including reported intranasal use on at least 3 occasions within the 12 months prior to screening and reported taking a dose equivalent to 30 mg oxycodone or more on at least one occasion in their life (Harris et al. 2014; Data on file).

The study design consisted of four phases: a screening phase (which included a naloxone challenge to determine opioid physical dependence); a qualification phase (to ensure adequate differential responsiveness to placebo vs. 30 mg oxycodone following intranasal administration and to ensure active treatment was adequately tolerated); a treatment phase; and a follow-up visit (2 to 4 days following the last treatment visit or after early withdrawal). The washout period was at least 12 hours between the naloxone challenge and the qualification phase, at least 3 days between the qualification and treatment phases, and at least 2 days between treatment visits (Harris et al. 2014).

Pharmacodynamic measures included a series of subjective rating scales or questionnaires on participants’ perceptions of their subjective state and nasal effects, observer ratings of intranasal irritation, and measurement of pupil size. Additionally, exposure to oxycodone following intranasal administrations was compared (Harris et al. 2014).

A Drug Liking visual analogue scale (VAS) was administered where subjects responded to questions with “strong disliking” to “strong liking” and a Take Drug Again VAS where subjects responded with “definitely not” to “definitely so”. Drug liking was measured on a continuous bipolar scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a continuous bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response (“definitely would not take drug again”) and 100 represents the strongest positive response (“definitely would take drug again”) (Harris et al. 2014).

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects’ nostrils occurred in 34% (n=10) of subjects with finely crushed OxyContin, compared with 7% (n=2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl. The intranasal administration of finely crushed OxyContin was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in **Table 29** (Harris et al. 2014; Data on file).

#### Table 26. Summary of Maximum Drug Liking (Emax) Data Following Intranasal Administration (Harris et al. 2014; Data on file)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **VAS Scale (100 mm)\*** | | **OxyContin (finely crushed)** | **Original OxyContin (finely crushed)** | **Oxycodone HCl (powdered)** |
| **Drug Liking** | Mean (SE) | 80.4 (3.9) | 94.0 (2.7)† | 89.3 (3.1)† |
| Median (Range) | 88 (36-100) | 100 (51-100) | 100 (50-100) |
| **Take Drug Again** | Mean (SE) | 64.0 (7.1) | 89.6 (3.9)† | 86.6 (4.4)† |
| Median (Range) | 78 (0-100) | 100 (20-100) | 100 (0-100) |

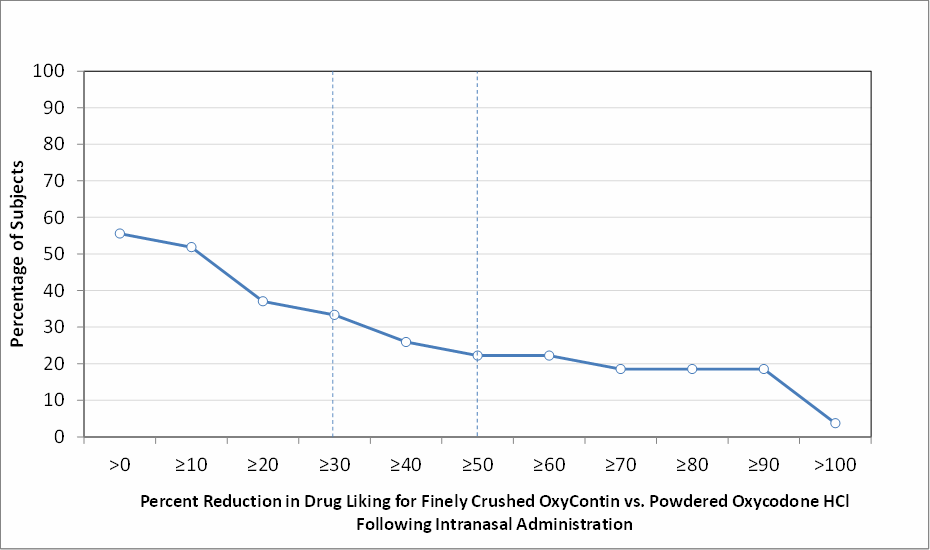
\* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

† Statistically significantly higher response (p ≤ 0.006) versus OxyContin

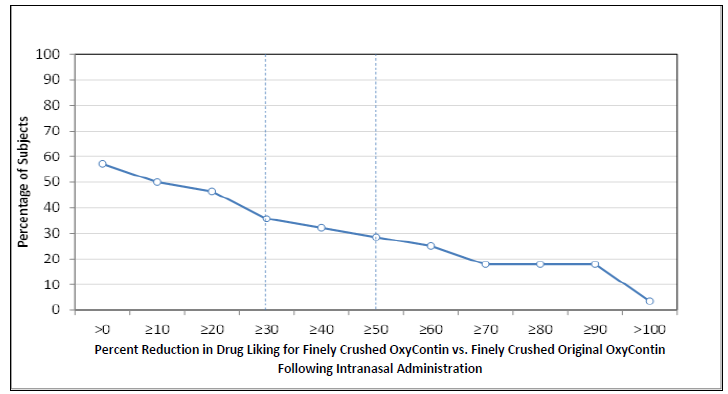
A post-hoc responder analysis of Emax for drug liking of finely crushed OxyContin compared to powdered oxycodone HCl found that among subjects who insufflated both treatments, a cumulative 56% (n = 15) had some reduction in drug liking, 44% (n = 12) had no reduction in liking, 33% (n = 9) had a reduction of at least 30%, and 22% (n = 6) had a reduction of at least 50% (**Figure 8**) (Harris et al. 2014).

A similar analysis comparing finely crushed OxyContin compared to finely crushed original OxyContin found that among subjects who insufflated both treatments, a cumulative 57% (n = 16) had some reduction in drug liking, 43% (n = 12) had no reduction in liking, 36% (n = 10) had a reduction of at least 30%, and 29% (n = 8) had a reduction of at least 50% (**Figure 9**) (Harris et al. 2014).

#### Figure 8. Percent Reduction Profiles for Emax of Drug Liking VAS for OxyContin vs. Oxycodone HCl Following Intranasal Administration (N=27) (Harris et al. 2014)



**Figure 9. Percent Reduction Profiles for Emax of Drug Liking VAS for OxyContin vs. Original OxyContin Following Intranasal Administration (N=28) (Harris et al. 2014)**



Overall, greater nasal irritation was seen with coarsely and finely crushed OxyContin compared to powdered oxycodone HCl, original OxyContin, and placebo. Finely crushed OxyContin had significantly higher Emax compared to placebo on measures of Need to Blow Nose (p = 0.017) and Nasal Congestion (p = 0.014), whereas powdered oxycodone HCl, original OxyContin, and coarsely crushed OxyContin did not. Both finely and coarsely crushed OxyContin had significantly higher Emax (p < 0.01) compared to powdered oxycodone HCl and original OxyContin on both of these measures, with the exception of coarsely crushed OxyContin vs. original OxyContin (p = 0.052) (Harris et al. 2014).

Analysis of pupillometry data showed mean minimum effect (Emin) values were significantly higher (reflecting smaller opioid-induced decreases in pupil size) for both finely and coarsely crushed OxyContin compared with those for powdered oxycodone HCl and original OxyContin, and significantly lower than that for placebo

(p < 0.001 for all comparisons). No notable differences were observed in pupil-size measurements over time following placebo treatment (Harris et al. 2014).

Pharmacokinetic analysis demonstrated that intranasal administration of finely crushed OxyContin resulted in lower mean oxycodone maximum plasma concentrations (Cmax; 29.4 ng/mL) compared to the intranasal administration of either finely crushed original OxyContin (59.6 ng/mL) or powdered oxycodone HCl (52.1 ng/mL). Time to achieve Cmax (Tmax) was greater following intranasal administration of OxyContin (2.1 hours) compared to the intranasal administration of either finely crushed original OxyContin (1.1 hours) or powdered oxycodone HCl (1.0 hours). Total systemic oxycodone exposure (AUC) was similar across treatments (Harris et al. 2014).

There were no deaths, serious adverse events, or severe treatment emergent adverse events (TEAEs). The overall incidence of reported TEAEs, from highest to lowest incidence, was 96.4% for finely crushed original OxyContin and 89.7% for powdered oxycodone HCl (positive controls), 86.2% for finely crushed OxyContin, 75.0% for coarsely crushed OxyContin, and 41.4% for placebo. Most TEAEs were of mild intensity. One participant experienced a moderately severe TEAE (respiratory depression following finely crushed original OxyContin intranasal administration). The most common TEAEs were consistent with the known effects of oxycodone and included euphoric mood, somnolence, nasal congestion, pruritus, and headache (Harris et al. 2014).

*Summary of In Vitro and In Vivo Data*

The in vitro data demonstrate that OxyContin has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route.

However, abuse of OxyContin by these routes, as well as by the oral route is still possible.

Michna E, Kirson NY, Shei A, Birnbaum HG, Ben-Joseph R. Use of prescription opioids with abuse-deterrent technology to address opioid abuse. *Curr Med Res and Opin*. 2014; 30(8): 1589-1598.

**OBJECTIVE**: The development of new formulations of extended-release (ER) opioids with abuse-deterrent technology attempts to deter prescription opioid abuse while maintaining appropriate access to care for pain patients. This study examined the degree to which some patients may avoid switching to reformulated ER opioids with abuse-deterrent technology and the extent to which those patients are more likely to be abusers.

**RESEARCH DESIGN AND METHODS**: We analyzed Truven MarketScan pharmacy and medical claims data following the introduction of two reformulated ER opioids with abuse-deterrent technology. Adults aged 18–64 who were continuous users of extended-release oxycodone HCl (ER oxycodone) or extended-release oxymorphone HCl (ER oxymorphone) in a 6 month period prior to the introduction of the respective reformulations of those products were identified and categorized based on whether they switched to the reformulation, switched to other ER/long-acting (LA) opioids (without abuse-deterrent technology), or discontinued ER/LA opioid treatment in a 6 month post-reformulation period. Abusers were identified using ICD-9-CM diagnosis codes for opioid abuse/dependence. Pearson’s chi-squared tests and Fisher’s exact tests were then used to compare rates of abuse between patients who avoided switching to a reformulated ER opioid. Sensitivity analyses examined several definitions used in this analysis.

**MAIN OUTCOME MEASURES**: ER/LA opioid utilization; rates of diagnosed opioid abuse.

**RESULTS**: A total of 31%–50% of patients avoided switching to reformulated ER opioids. Rates of diagnosed opioid abuse were higher among these patients compared to patients who transitioned to the reformulated ER opioids.

**LIMITATIONS**: Due to the observational research design, caution is warranted in causal interpretation of the findings. The study was conducted among commercially insured continuous ER oxycodone or ER oxymorphone users; future research should consider additional patient populations, such as non-continuous users and those without commercial insurance (i.e., Medicare, Medicaid, uninsured).

**CONCLUSIONS**: Some patients switched to other ER/LA opioids without abuse-deterrent technology or discontinued ER/LA opioid treatment when their existing ER treatment was reformulated. Rates of opioid abuse were higher among patients who switched to other ER/LA opioids or discontinued ER/LA opioid treatment, suggesting that abusers may seek more easily abuseable alternatives such as prescription opioids without abuse-deterrent technology.

Rossiter LF, Kirson NY, Shei A, et al. Medical cost savings associated with an extended-release opioid with abuse-deterrent technology in the U.S. *J Med Econ*. 2014; 17(4):279-287. <http://informahealthcare.com/doi/pdf/10.3111/13696998.2014.897628>

**OBJECTIVES**: In the US, prescription opioids with technology designed to deter abuse have been introduced to deter drug abuse without hindering appropriate access for pain patients. The objective of this study was to estimate changes in medical costs following the introduction of a new formulation of extended-release (ER) oxycodone HCl (oxycodone) with abuse-deterrent technology in the US.

**METHODS**: Health insurance claims data were used to estimate changes in rates of diagnosed opioid abuse among continuous users of extended-release opioids (EROs) following the introduction of reformulated ER oxycodone in August 2010. This study also calculated the excess medical costs of diagnosed opioid abuse using a propensity score matching approach. These findings were integrated with published government reports and literature to extrapolate the findings to the national level. All costs were inflated to 2011 US dollars.

**RESULTS**: The introduction of reformulated ER oxycodone was associated with relative reductions in rates of diagnosed opioid abuse of 22.7% (p < 0.001) and 18.0% (p = 0.034) among commercially-insured and Medicaid patients, respectively. There was no significant change among Medicare-eligible patients. The excess annual per-patient medical costs associated with diagnosed opioid abuse were $9456 (p < 0.001),

$10,046 (p < 0.001), and $11,501 (p < 0.001) for commercially-insured, Medicare-eligible, and Medicaid patients, respectively. Overall, reformulated ER oxycodone was associated with annual medical cost savings of

∼$430 million in the US.

**LIMITATIONS**: Because of the observational research design of this study, caution is warranted in any causal

interpretation of the findings. Portions of the study relied on prior literature, government reports, and assumptions to extrapolate the national medical cost savings.

**CONCLUSIONS**: This study provides evidence that reformulated ER oxycodone has been associated with reductions in abuse rates and substantial medical cost savings. Payers and policy-makers should consider these benefits as they devise and implement new guidelines and policies in this therapeutic area

Kirson NY, Shei A, White AG, Birnbaum HG, Ben-Joseph R, Rossiter LF, Michna E. Societal economic benefits associated with an extended-release opioid with abuse-deterrent technology in the U.S. *Pain Medicine*. 2014; 15(9):1450-1454. <http://dx.doi.org/10.1111/pme.12489>.

The objective of this study was to estimate the indirect cost savings associated with introduction of the ADF for ER oxycodone by building on the $430 million in medical cost savings reported by [Rossiter](#_bookmark37) et al. (2014), as medical cost savings alone are an underestimate of the full societal economic benefits of the abuse-deterrent formulation (ADF) of ER oxycodone.

The authors assumed that the ADF of ER oxycodone would have the same proportional effect on abuse- related indirect costs as abuse-related medical costs. The authors calculated the percent reduction in abuse- related medical costs by dividing the abuse-related medical cost savings of the ADF of ER oxycodone from Rossiter et al. (2014) by the excess medical and drug costs for opioid abuse patients from Birnbaum et al. (2011). The authors then applied the percent reduction in abuse-related medical costs to the indirect costs for opioid abuse patients from Birnbaum et al. (2011) to estimate the indirect cost savings associated with the introduction of the ADF of ER oxycodone.

Kirson et al. estimated $605 million (2011 USD) in indirect cost savings associated with the introduction of the ADF for ER oxycodone. These indirect cost savings were due to reductions in workplace costs ($476 million), reductions in criminal justice costs ($96 million), and reductions in the excess medical and drug costs for caregivers of opioid abuse patients ($33 million). Combining the indirect cost savings of $605 million from this study and the medical cost savings of $430 million from Rossiter et al. (2014) yields total societal cost savings associated with the introduction of the ADF of ER oxycodone of approximately $1.0 billion.

Ben-Joseph R, Chen CC, De AP, Wade RL, Shah D. Consequences of patient access restriction to branded oxycodone hydrochloride extended-release tablets on healthcare utilization and costs in US health plans. *J Med Econ.* 2014; 17:708-718.

**OBJECTIVES**: To evaluate the impact of increased access restrictions to branded oxycodone hydrochloride extended release tablets (oxycodone HCl ER), on healthcare utilization and costs in patients using extended- release and long-acting opioids (ER/LA opioids) from the health plan perspective during the period from 1/1/2009 to 6/30/2012.

**METHODS**: This retrospective cohort study analyzed claims data for adult patients from US plans that increased oxycodone HCl ER access restrictions. Study groups were segmented into commercial and Medicare payers, and by prior authorization (PA) and tier change (TC) restrictions. Six-month outpatient visits and prescription utilization and costs were evaluated during the pre- and post-access restriction periods using a bootstrapped t-test and regression to test the differences.

**RESULTS**: Mean 6-month post-restriction combined pharmacy and outpatient visit costs were $1131 (p<.001),

$660 (p=0.009), $699 (p<.001), and $564 (p<.001) higher than pre-restriction costs in commercial PA, commercial TC, Medicare PA, and Medicare TC groups, respectively. Outpatient visits accounted for the greatest proportion of increased costs in the access restriction groups.

**CONCLUSIONS**: The results of this study suggest that oxycodone HCl ER access restrictions such as PA and TC may increase medical costs without an offsetting savings in pharmacy costs.

Zhou B, Wang J, Yan Z, Shi P, Kan Z. Liver cancer: effects, safety, and cost-effectiveness of controlled- release oxycodone for pain control after TACE. *Radiology.* 2012 Mar;262(3):1014-21.

See [summary](#_bookmark24) in section 3.1.1, Studies in Patients with Postoperative Pain.

Hartung DM, Middleton L, Haxby DG, et al. Rates of adverse events of long-acting opioids in a state Medicaid program. *Ann Pharmacother*. 2007;41(6):921-928.

This retrospective observational cohort evaluated the risk of serious adverse events among Oregon fee-for- service Medicaid recipients prescribed long-acting opioids (LAO).

Subjects were included if they had at least one prescription of at least 28 days’ supply between January 1, 2000, and December 31, 2004, and at least 180 days of continuous Medicaid fee-for-service program eligibility prior to their first index fill.

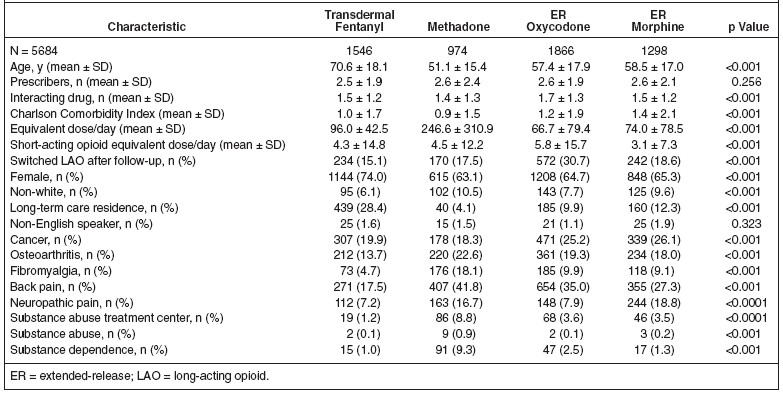
Four cohorts were established based on the index prescription fill, defined as the first prescription claim during the study period for following LAOs: (1) methadone (Dolophine and generics), (2) extended-release (ER) oxycodone (OxyContin and generics), (3) ER morphine (MS Contin, Oramorph, Kadian, Avinza, and generics), and (4) transdermal fentanyl (Duragesic and generics). Continuous exposure was defined as successive LAO prescriptions at a maximum interval of 31 days from the last prescription’s days’ supply. Subjects in the ER morphine cohort were used as the reference cohort.

The primary outcome was the first administrative claim for an emergency department (ED) visit or hospitalization with a diagnostic code suggesting an opioid-related adverse event. Specifically, ED and hospitalizations with an ICD-9 diagnosis code for poisoning by opiates and related narcotics (9650x); alteration of consciousness (7800x); malaise, fatigue, or lethargy (7807x); respiratory failure (51881, 51882); or constipation (5640x) were identified. Hospitalizations were identified using the Diagnosis-Related Group coding system. The rates of all-cause ED encounters and hospitalizations, as well as encounters for opioid- related adverse events were compared between cohorts. Estimated differences in the rate of all-cause mortality were evaluated based on data from the monthly vital statistics report provided by the Oregon Center for Health Statistics.

Cox proportional hazards models were used to adjust the following covariates: age, race, sex, long-term care residence, number of unique prescribers, disease severity, concomitant prescription claims for drugs with known pharmacodynamic interactions with LAOs, the type of presumed pain diagnosis, and history of opioid dependence, abuse, or enrollment in a substance abuse treatment program. Pain diagnosis were identified using ICD-9 codes from medical encounter claims processed one year before and after a subject’s cohort entry date and included osteoarthritis, back pain (dorsopathies), peripheral nervous system disorders, fibromyalgia, and neoplasm. The prevalence of opioid dependence, abuse, or enrollment in a state-monitored substance abuse program was also quantified and adjusted for. For each cohort, the average daily dose of long- and short-acting opioids was calculated and converted to a morphine-equivalent daily dose. Also quantified was whether a different LAO was started subsequent to the end of the patients’ original LAO exposure (LAO change). In addition, the occurrence of outcomes in subjects with a diagnosis of cancer and those without cancer who had a diagnosis of osteoarthritis, fibromyalgia, back pain, or neuropathy was evaluated.

Over the study period, a total of 5,684 subjects had an index prescription for an LAO with a minimum 28 days’ supply, with the largest cohort prescribed ER oxycodone and the smallest prescribed methadone. Multiple statistically significant differences among the cohorts’ demographics were noted (**Table 30**).

#### Table 30. Cohort Demographics

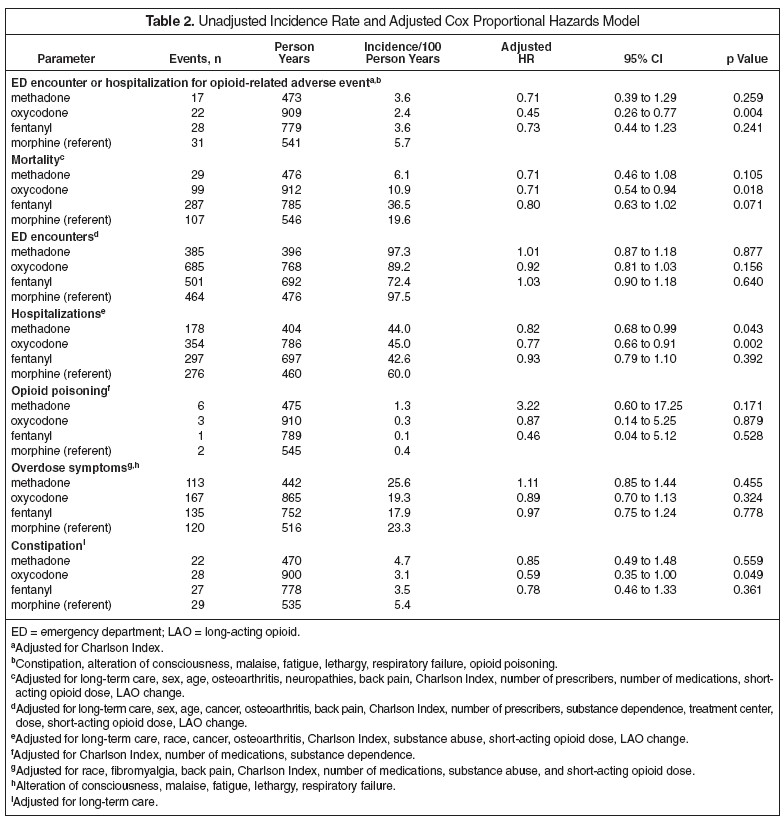


The absolute incidence of the various outcomes, as well as adjusted hazard ratios generated from multivariate Cox proportional hazards models are shown in **Table 31**. For the primary outcome of time to first ED or hospitalization for opioid-related adverse events, subjects in the oxycodone ER cohort were 35% less likely to have an event compared with the morphine ER cohort. A correction was later published stating subjects in the oxycodone ER cohort were 55% less likely to have an event compared with the morphine ER cohort and not 35% as originally reported (*Ann Pharmacother* [Letter]. 2007). Subjects in the oxycodone ER cohort were also 29% less likely to die compared to subjects in the morphine ER cohort. There were no significant differences between cohorts in the risk of any ED encounter. However, subjects prescribed methadone or oxycodone ER were significantly less likely to be hospitalized compared with morphine ER by 18% and 23%, respectively.

There were no significant differences between cohorts in the risk of symptoms of overdose or the risk of being diagnosed with opioid poisoning. The diagnosis of constipation was 41% less likely in subjects prescribed oxycodone ER compared to subjects prescribed morphine ER.

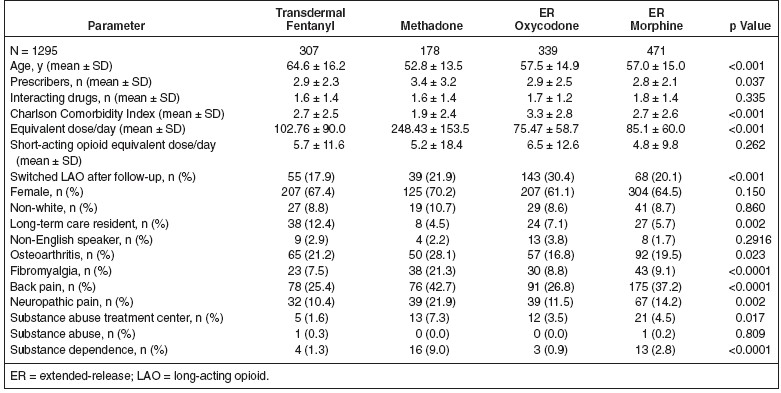
Absolute risk reductions were estimated by subtracting the incidence rates for a given outcome for each cohort from the reference cohort. In absolute and unadjusted terms, subjects prescribed oxycodone ER experienced about 3.3 ED encounters or hospitalizations for opioid-related adverse events, 8.4 ED encounters, 15.0 hospitalizations, and 8.7 deaths per 100 person years less than those prescribed morphine ER (**Table 31**).

#### Table 31. Unadjusted Incidence Rate and Adjusted Cox Proportional Hazards Model

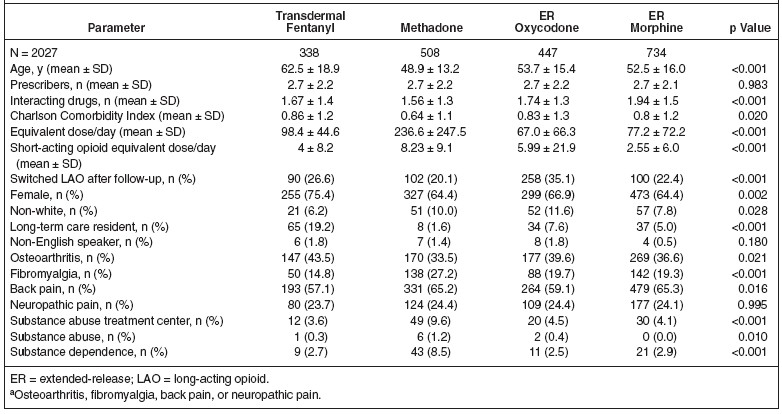


Of the total population, 1,295 subjects were identified with a cancer diagnosis (**Table 32**) and 2,027 had a noncancer pain diagnosis (**Table 33**). A summary of outcomes measured in the cancer and noncancer subgroups is shown in **Table 34**. Overall, the hazard ratio (HR) observed for subjects with a cancer diagnosis were similar to estimates for the total population. However, subjects with a diagnosis of cancer in the oxycodone ER cohort had a significantly lower risk of hospitalization than those prescribed morphine ER. Among subjects with noncancer pain diagnoses, the risk of several adverse outcomes differed qualitatively for the risk from the cancer cohort and the overall population. The transdermal fentanyl group had a significant increase in the risk for ED encounter compared with the morphine ER group. The risk of experiencing a symptom of overdose was 57% higher in the methadone group compared with the morphine ER group.

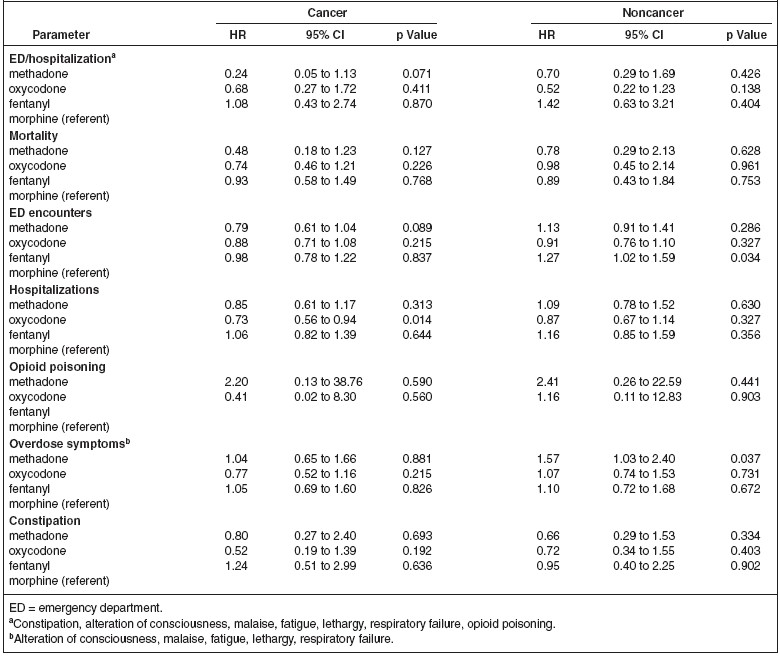
#### Table 32. Demographics of Subjects with Cancer



**Table 33. Demographics of Subjects with Other Pain-Related Conditions\***



**Table 27. Adjusted Cox Proportional Hazard Models Among Patients with Specific Pain Diagnoses**



Marshall DA, Strauss ME, Pericak D, et al. Economic evaluation of controlled-release oxycodone vs oxycodone-acetaminophen for osteoarthritis pain of the hip or knee. *Am J Manag Care*. 2006;12(4):205-214.

The purpose of this prospective, active-controlled, randomized, naturalistic, open-label 4-month trial was to examine, in routine practice, the effectiveness and cost-effectiveness of controlled-release oxycodone (CRO) compared to oxycodone/acetaminophen (oxy/APAP) added to a platform of usual care in patients with moderate to severe pain from osteoarthritis (OA) of the hip or knee.

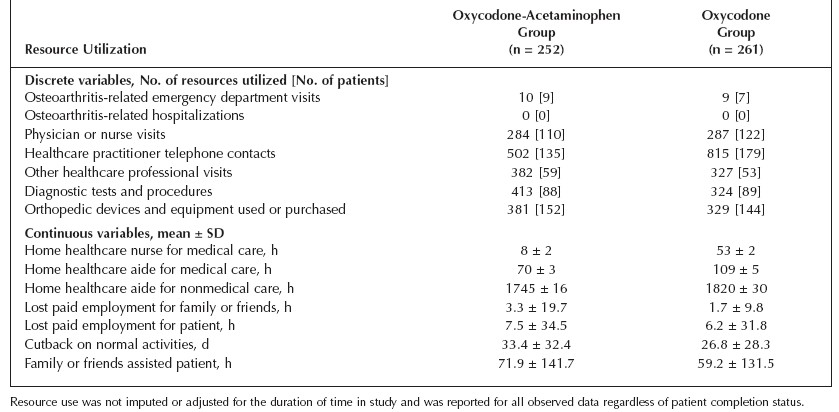
The study population consisted of patients ≥40 years of age with moderate to severe OA pain of the hip or knee for at least 3 months that was not adequately controlled with short-acting opioid therapy. Radiographic evidence of OA within the past 2 years also had to be shown for enrollment in the study. Patients had to have taken ≥2 tablets of short-acting opioid per day (equivalent daily dose of ≥10 mg of oxycodone) for moderate to severe OA pain for 4-7 days before randomization.

Data were collected at the physician’s office at baseline and at study termination (month 4). Patients received either CRO 10 mg every 12 hours or oxy/APAP 5/325 mg every 4 to 6 hours as needed. For outcomes and health resource utilization data the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Likert 3.0 and the Health Utilities Index 3 (HUI3) health-related QOL (HRQOL) instruments were administered at baseline and at months 1, 2, 3, and 4 by telephone interview. For the cost-effectiveness analysis (CEA), effectiveness was measured as the proportion of “patients improved,” defined per the American College of Rheumatology guidelines as having at least 20% improvement from baseline to month 4 in the WOMAC pain score. The overall HUI3 utility score was used to calculate the quality-adjusted-life-years (QALYs) for the cost- utility analysis (CUA). All health resource utilization data was collected weekly by telephone and costed using Medicare reimbursement and medications were costed using the *Drug Topics Red Book* adjusted to 2003 US dollars.

To respond to the interest of diverse audiences, analyses were evaluated from the healthcare system (HCS) and societal perspectives. The HCS perspective included costs for medications, healthcare visits, hospitalizations and emergency department visits, diagnostic tests and procedures, home healthcare services, and assistive devices. The societal perspective also included time lost from paid work and unpaid regular activities for the patient and family and friends. The CEA was measured as cost per patient improved (over 4 months) and QALYs gained from societal and healthcare perspectives using generic oxy/APAP (base case). Uncertainty was evaluated using multiple one-way sensitivity analyses and cost-effectiveness acceptability curves (CEAC).

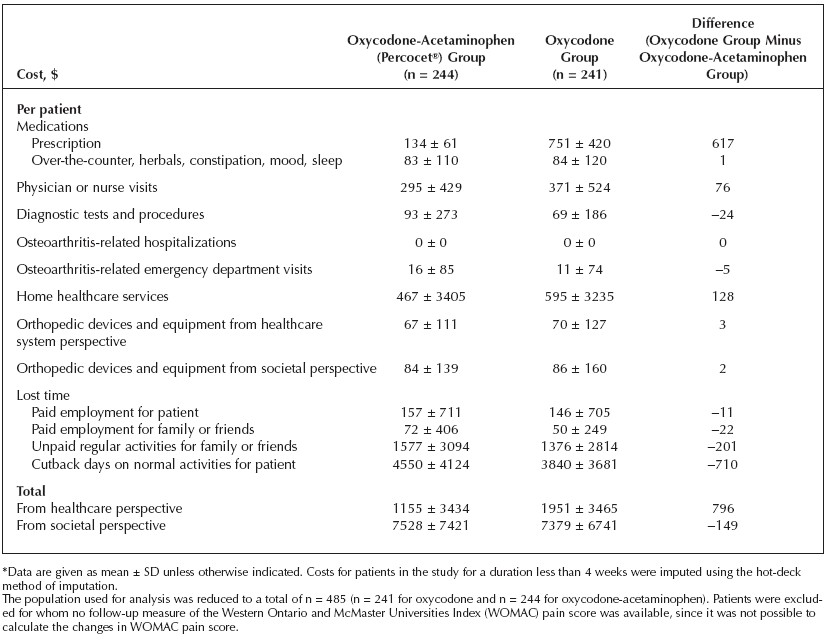
Five hundred thirteen patients were included in the intent-to-treat analysis (n=261, CRO; n=252, oxy/APAP group). During the 4 month period with regard to health resource utilization and costs, more CRO patients than oxy/APAP patients had used more service hours of a home health aide or nurse. Patients in the oxy/APAP group lost more hours from employment and from normal activities than patients in the CRO group. Time lost was the largest cost driver in the analysis from the societal perspective (**Table 35**).

#### Table 35. Health Resource Utilization During 4 Months



For patients in the CRO group, the total OA-related HCS costs per patient for months 1 to 4 were greater compared to the oxy/APAP group ($1,951 vs. $1,155), driven by prescription medication costs ($751 vs. $134) and home healthcare service costs ($595 vs. $467). The total OA-related societal costs per patient for months 1 to 4 were lower for patients in the CRO group compared to the oxy/APAP group ($7,379 vs. $7,528, p=0.33), driven by costs associated with time lost from activities in the oxy/APAP group (**Table 36**).

#### Table 28. Osteoarthritis-related Costs During 4 Months\*

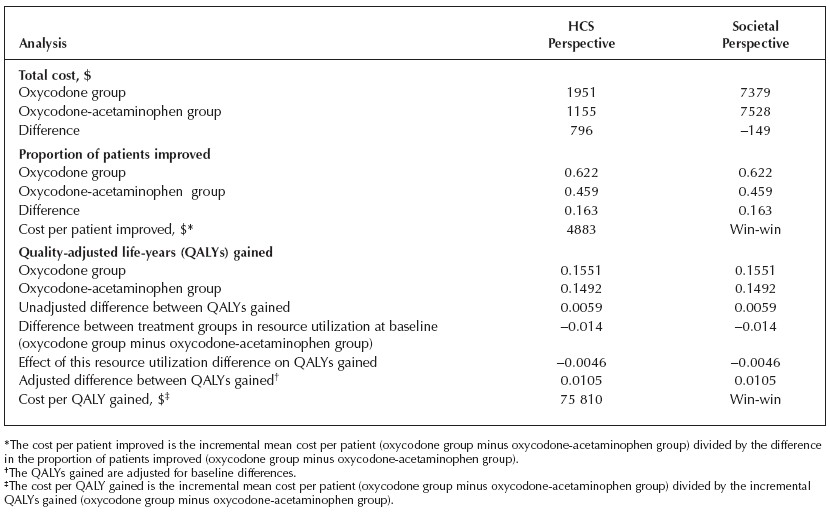


With regard to effectiveness, the CRO group had a larger proportion of patients who improved compared with patients in the oxy/APAP group (62.2% vs. 45.9%, p < 0.001). Patients in the CRO group also gained 0.0105 QALYs during the 4-months compared to the oxy/APAP group (p=0.17). The base-case incremental cost- effectiveness analysis from the HCS perspective showed that the incremental mean cost per patient was $796, and the difference in proportion of patients improved was 0.163. Therefore, CRO was more costly and more effective than oxy/APAP, with incremental cost-effectiveness ratio of $4,883 per patient improved. From the societal perspective, the incremental mean cost per patient was $149 less in the CRO group compared with the oxy/APAP group. Therefore, CRO was less costly and more effective than the oxy/APAP group (**Table 37**).

For the base-case incremental cost-utility analysis illustrated from the HCS perspective, the incremental mean cost per patient was $796, and 0.0105 QALYs were gained in the CRO group compared to the oxy/APAP group. Therefore, CRO was more costly and more effective than oxy/APAP, with an incremental cost-utility ratio of $75,810 per QALY gained. From the societal perspective, the incremental mean cost per patient was

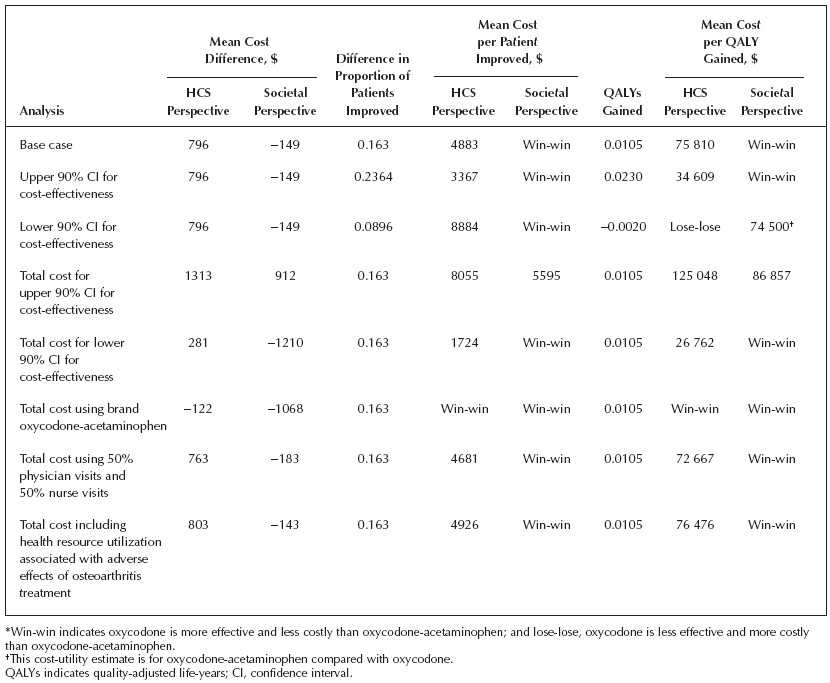
$149 less in the CRO group compared with the oxy/APAP group. Since CRO was less costly and more effective than oxy/APAP, an incremental cost-utility ratio was not calculated (**Table 37**).

#### Table 37. Base-Case Analyses From the Healthcare System (HCS) and Societal Perspectives Among 241 Patients in the Oxycodone Group and 244 Patients in the Oxycodone-Acetaminophen Group

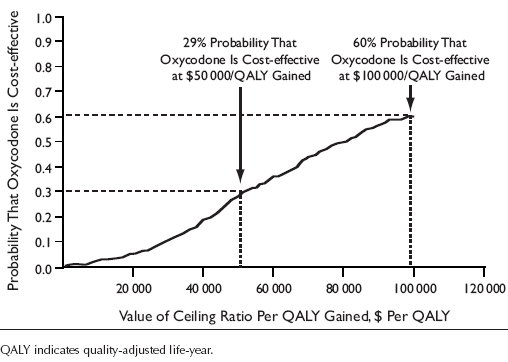


In the one-way sensitivity analysis from the HCS perspective, the cost-effectiveness analysis results ranged from a single dominant result to $8,884 per patient improved. From the societal perspective, six of seven results fell in win-win quadrants (**Table 38**). With respect to the cost-utility analysis, the results of the one-way sensitivity analysis from the HCS perspective, varied from CRO being dominated (lose-lose quadrant) to CRO dominating (win-win quadrant) (**Table 38**). Five of seven results fell in the upper right quadrant of the cost- effectiveness plane, with incremental cost-utility ratios ranging from $26,762 to $125,048 per QALY gained. The probability that CRO was cost-effective was 29% at the decision threshold of $50,000 per QALY gained and 60% at the $100,000 per QALY gained (**Figure 10**). From the societal perspective, the cost-utility results also varied from oxycodone being dominated (lose-lose quadrant) to CRO dominating (win-win quadrant). Five of seven results indicated that CRO dominated (win-win quadrant). The probability that oxycodone was cost- effective was 77% at the decision threshold of $50,000 per QALY gained and 84% at $100,000 per QALY gained (**Figure 11**).

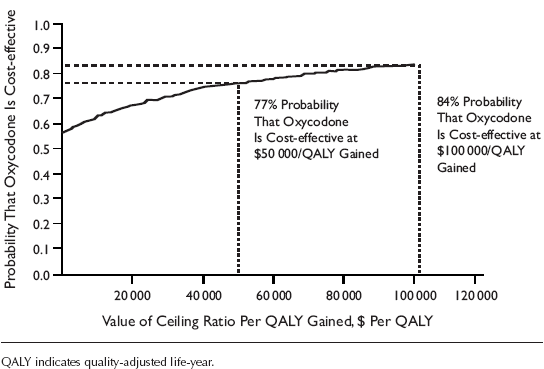
#### Table 298. Cost-effectiveness and Cost-Utility Analyses From the Healthcare System (HCS) and Societal Perspectives Among 241 Patients in the Oxycodone Group and 244 Patients in the Oxycodone-Acetaminophen Group: One-Way Sensitivity Analyses\*



**Figure 10. Cost-effectiveness Acceptability Curve for the Cost-Utility Analysis From the Healthcare System Perspectives**



**Figure 11. Cost-effectiveness Acceptability Curve for the Cost-Utility Analysis From the Social Perspective**



Overall, the study found that from a societal perspective, CRO was more effective and less costly than oxy/APAP. From the healthcare perspective, CRO (compared with generic oxy/APAP) fell within the acceptable range of cost-effectiveness between $50,000 and $100,000 per QALY gained.

Berger A, Hoffman DL, Goodman S, et al. Therapy switching in patients receiving long-acting opioids. *Ann Pharmacother*. 2004;38(3):389-395.

The purpose of this retrospective study using a large U.S. healthcare claims database was to examine rates of therapy switching in clinical practice among patients beginning treatment with controlled-release (CR) oxycodone, transdermal fentanyl, or CR morphine sulfate and to compare healthcare charges for patients who switched long-acting opioid therapy versus those who did not. In this study, therapy switching was defined as receipt during follow-up of a long-acting opioid other than the one received initially (designated as the index date).

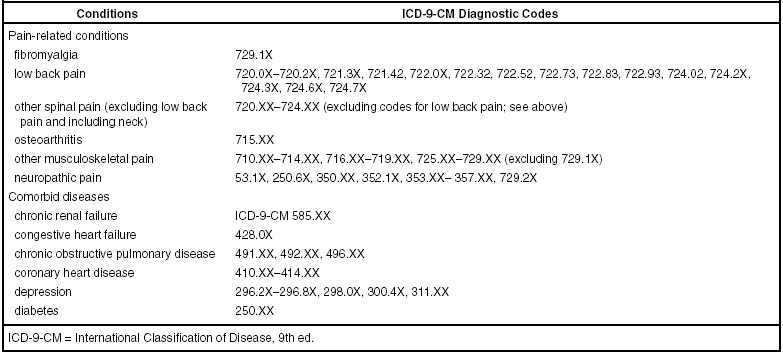
The claims database used for this study was Protocare Sciences Managed Care Database. The database is comprised of paid institutional, provider, and outpatient pharmacy claims derived from a variety of private healthcare plans. The database contains healthcare claims and enrollment data for approximately 3 million persons annually residing in over 20 states. Approximately one-quarter of persons in the database are aged

≥65 years. The database includes patient demographic, eligibility, and vital status information, inpatient and outpatient diagnoses (in ICD -9-CM format), inpatient and outpatient procedure information (in ICD -9-CM, Physician’s Current Procedural Terminology, 4th ed. [CPT-4], and Health Care Financing Administration Common Procedure Coding System [HCPCS] formats), outpatient drugs (identified by National Drug Code [NDC]) and associated therapy-days dispensed, billed charges, and dates of service for drugs and medical services.

Patients were included in the study, if they began therapy with CR oxycodone, transdermal fentanyl, or CR morphine sulfate between July 1, 1998, and December 31, 1999. Patients were excluded if they had (1) received CR oxycodone, transdermal fentanyl, or CR morphine sulfate during the 6-month period preceding their index date (pretreatment), (2) received multiple long-acting opioids on their index date, (3) received <30 days of long-acting opioid therapy during the 6-month period following their index date (follow-up), (4) were not continuously eligible for health and drug benefits during pretreatment and follow-up, or (5) were enrolled in a Medicare supplemental or capitated health plan (the database does not include complete claims histories for these persons).

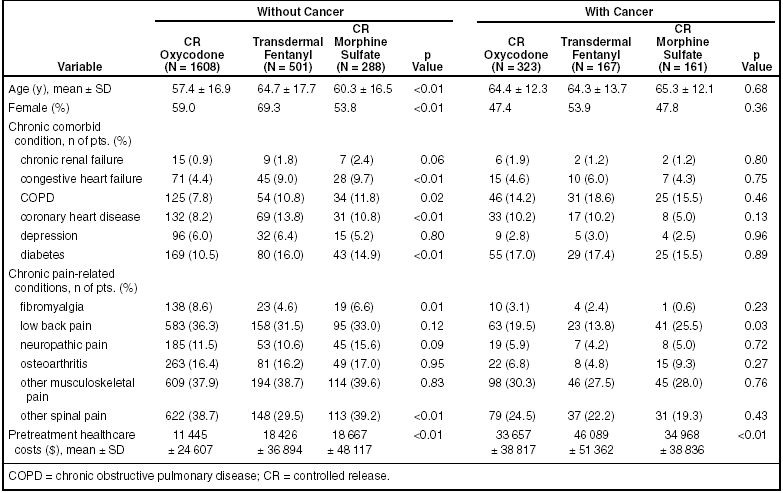
The date of each patient’s initial receipt of one of these agents was designated their index date, and patients were categorized into treatment groups according to the agent they received on this date. All medical and pharmacy claims were compiled for each patient over the 6-month period following therapy initiation and compared the incidence of therapy switching among patients receiving the agents. The study sample was stratified according to whether patients had cancer (except squamous or basal cell skin carcinoma, as these rarely cause significant pain) (ICD-9-CM diagnosis codes 140.XX–172.XX, 174.XX–208.XX) (**Table 39**), since the patterns of therapy switching may differ for patients with cancer versus those not having cancer.

#### Table 39. ICD-9-CM Diagnostic Codes Used in Determining Prevalence of Pain-Related and Comorbid Conditions



A total of 1,931, 668, and 449 patients were identified who began therapy with CR oxycodone, transdermal fentanyl, and CR morphine sulfate, respectively. Out of the total population, 16.7% (CR oxycodone), 25.0% (transdermal fentanyl) and 35.9% (CR morphine sulfate) had cancer (**Table 40**).

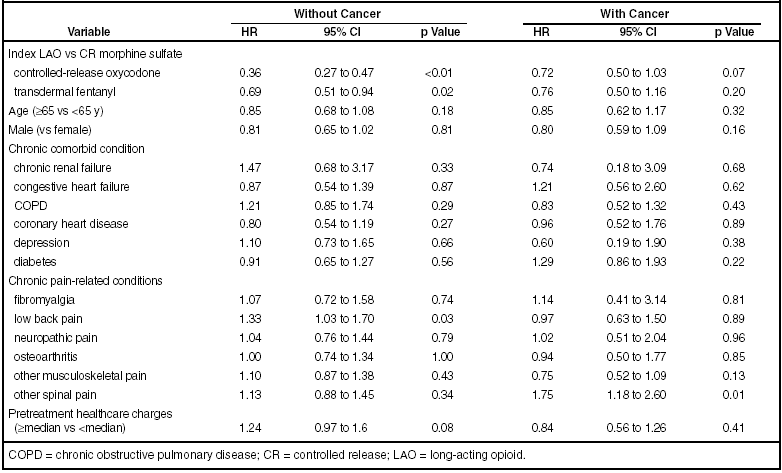
#### Table 40. Characteristics of Patients Receiving Long-Acting Opioids by Presence of Cancer



Time to switching was assessed in terms of the number of days between the index date and the date of first receipt of another long-acting opioid. Attention was focused on the first therapy switch only. Estimates of time

to switch and the cumulative percentage of patients switching in the three groups were generated using Kaplan–Meier techniques. The corrected group-prognosis method was employed to adjust these estimates for differences in selected covariates, including age (≥65 years vs. younger), gender, the presence of selected chronic pain-related conditions and other chronic comorbidities, and pretreatment healthcare charges (≥median vs. <median). The probability of therapy switching was assessed using multivariate Cox proportional hazards models (**Table 41**). Covariates entered into these models were as noted above. To compare the charges of patients who switched therapy versus those who did not, patients were pooled across the three treatment groups and restratified according to whether they switched therapy during follow-up.

#### Table 41. Multivariate Cox-Proportional Hazards Analysis of Factors Associated with Long-Acting Opioid Switching by Presence of Cancer



Among patients without cancer, rates of therapy switching at 6 months were 10.6% for CR oxycodone, 19.0% for transdermal fentanyl, and 26.0% for CR morphine sulfate. Adjusted for covariates using the corrected group-prognosis method, similar results were obtained (10.5%, CR oxycodone vs. 19.6%, transdermal fentanyl vs. 26.6%, CR morphine sulfate). Median time to switching was 63 days for CR oxycodone, 57 days for transdermal fentanyl, and 44 days for CR morphine sulfate.

Among patients with cancer, rates of therapy switching were 23.8% for CR oxycodone, 24.6% for transdermal fentanyl, and 29.8% for CR morphine sulfate. On an adjusted basis, similar results were obtained (23.6%, CR oxycodone vs. 24.2%, transdermal fentanyl vs. 31.1%, CR morphine sulfate). Median time to switching was 77 days for CR oxycodone, 52 days for transdermal fentanyl, and 26 days for CR morphine sulfate.

Among patients without cancer (n=2,397), 341 (14.2%) switched long-acting opioid therapy during follow-up. Those who switched therapy were more likely to be women and to have low back pain and other spinal pain (**Table 42**). Adjusted mean total healthcare charges during follow up were $9,666 higher among those who switched therapy compared with those who did not (**Table 43**). Inpatient care accounted for 59.1% of the total charges among patients who switched therapy and 54.5% among those who did not. Charges for pain-related

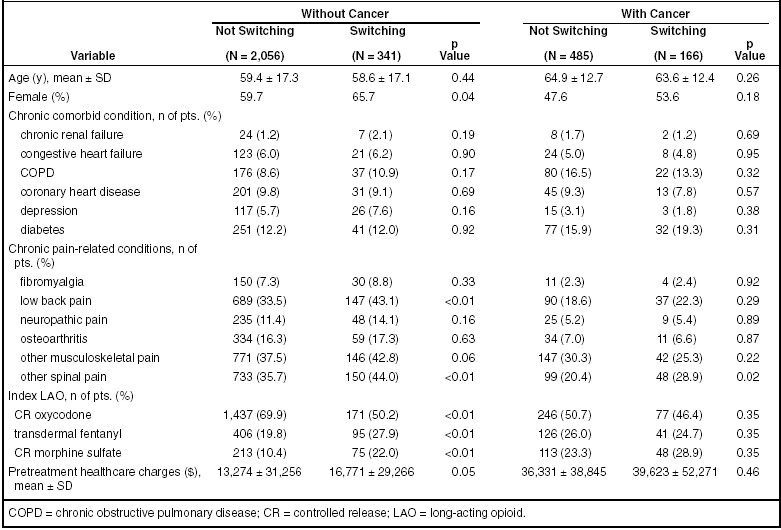
pharmacotherapy were greater among patients who switched long-acting opioid therapy compared with those who did not.

Among patients with cancer (n=651), 25.5% switched therapy during follow-up. Patients who switched therapy were more likely to have other spinal pain compared with those who did not switch. Adjusted mean total healthcare charges during follow-up were $18,641 higher among those who switched therapy compared with those who did not. Inpatient care accounted for 48.2% of total charges among patients who switched therapy and 42.2% among those who did not. Charges for pain-related pharmacotherapy were also greater among patients who switched long-acting opioid therapy.

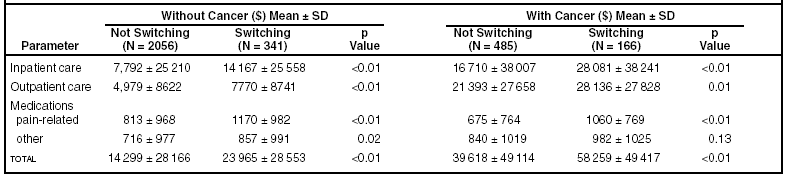
Patients beginning treatment with CR oxycodone or transdermal fentanyl are less likely to switch therapy than those treated initially with CR morphine sulfate. Among patients with cancer, those receiving CR oxycodone or transdermal fentanyl were approximately 25% less likely to switch therapy, although this result did not achieve statistical significance. Patients who switch long-acting opioid therapy have significantly higher healthcare charges than those who do not. This finding persists after adjustment for covariates such as age, preexisting diagnoses, and pretreatment healthcare charges. Charges for inpatient and outpatient care, as well as for pain-related medications, were significantly higher for cancer and noncancer patients who switched therapy.

While we cannot establish causality with our study design, our findings do raise the interesting possibility that better pain management may lead to reduced rates of therapy switching and lower healthcare costs.

#### Table 42. Characteristics of Patients Receiving Long-Acting Opioids Switching and Not Switching Therapy by Presence of Cancer



**Table 30. Healthcare Changes for Patients Receiving Long-Acting Opioids Switching and Not Switching Therapy by Presence of Cancer**



## vidence Table Spreadsheets of all Published and Unpublished Studies

#### Table 44. Summary of OxyContin Economic Studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Study Design and Treatments Compared** | **Time Horizon and Demographics** | **Model Inputs and Data Sources** | **Results: Base Case, Sensitivity Analysis and Limitations** |
| Zhou B, Wang J, Yan Z, Shi P, Kan Z. Liver cancer: effects, safety, and cost- effectiveness of controlled- release oxycodone for pain control after TACE.  *Radiology*. 2012;262(3):1014  -21. | Prospective, Randomized, Double-blind, Placebo- controlled study  Three groups:  (1) 20 mg controlled-release oxycodone (CRO) 1 hour before TACE (T0) and 12 (T12) and 24 (T24) hours after T0; (2) 10 mg CRO, given at the same intervals as group 1; (3) placebo of 100 mg vitamin C, given at the same intervals as group 1  N=210  Group 1, n=70  Group 2, n=70  Group 3, n=70 | 3 days  Patients with confirmed diagnosis of liver cancer, number of tumors ≤3, tumor diameter >3 cm and <8cm | Cost-effectiveness (mean analgesic cost and hospital stay) | * Analgesic cost and hospital stay in groups 1 and 2 was significantly less than in group 3 (median analgesic cost, Chinese Yuan: 37.0, group 1 vs. 19.6, group 2 vs. 43.4, group 3 [p=0.002]; mean hospital stay, days: 4.2±0.4, group 1 vs. 4.3±0.4, group 2 vs. 5.1±1.1, group 3 [p<0.001]); cost was significantly lower in group 2 than in group 1 (p=0.001). |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Study Design and Treatments Compared** | **Time Horizon and Demographics** | **Model Inputs and Data Sources** | **Results: Base Case, Sensitivity Analysis and Limitations** |
| Hartung DM, Middleton L, Haxby DG, et al. Rates of adverse events of long- acting opioids in a state Medicaid program. *Ann Pharmacother*. 2007;41(6):921-  928. | Retrospective, observational cohort study  4 cohorts: (1) methadone (Dolophine and generics); (2) ER oxycodone (OxyContin and generics); (3) ER morphine (MS Contin, Oramorph, Kadian, Avinza, and generics); (4) transdermal fentanyl (Duragesic and generics).  ER morphine served as reference  N=5,684 | Subjects were included if they had at least one prescription of at least 28 days’ supply between January 1, 2000,  and December 31, 2004, and at least 180 days of continuous Medicaid fee-for- service program eligibility prior to their first index fill. | Administrative claims for an ED visit or hospitalization with a diagnostic code suggesting an opioid-related AE were analyzed  Hospitalizations were identified using the Diagnosis-Related Group coding system.  Rates of all-cause ED encounters and hospitalizations, as well as encounters for opioid-related AEs were compared between cohorts.  Estimated differences in the rate of all-cause mortality were evaluated based on data from the monthly vital statistics report provided by the Oregon Center for Health Statistics.  ARR were estimated by subtracting the incidence rates for a given outcome for each cohort from the reference cohort. | * Time to first ED or hospitalization for opioid-related adverse events (primary outcome): Subjects in the oxycodone ER cohort were 35% less likely to have an event compared with the morphine ER cohort. A correction was later published stating subjects in the oxycodone ER cohort were 55% less likely to have an event compared with the morphine ER cohort and not 35% as originally reported. * Oxycodone ER cohort patients were 29% less likely to die compared to those in morphine ER cohort. * No significant differences between cohorts in the risk of any ED encounter, risk of symptoms of overdose or the risk of being diagnosed with opioid poisoning * Subjects prescribed methadone or oxycodone ER were significantly less likely to be hospitalized compared with morphine ER by 18% and 23%, respectively. * The diagnosis of constipation was 41% less likely in subjects prescribed oxycodone ER compared to subjects prescribed morphine ER. * In absolute and unadjusted terms, subjects prescribed oxycodone ER experienced about 3.3 ED encounters or hospitalizations for opioid-related adverse events, 8.4 ED encounters, 15.0 hospitalizations, and 8.7 deaths per 100 person years less than those prescribed morphine ER |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Study Design and Treatments Compared** | **Time Horizon and Demographics** | **Model Inputs and Data Sources** | **Results: Base Case, Sensitivity Analysis and Limitations** |
| Marshall DA, Strauss ME, Pericak D, et al. . Economic evaluation of controlled- release oxycodone vs. oxycodone- acetaminophen for osteoarthritis pain of the hip or knee. *Am J Manag Care*.  2006;12:205-214. | Prospective, active-controlled, randomized, naturalistic, and open-label study  Controlled-release oxycodone (CRO) cost-effectiveness compared to oxycodone/ APAP (oxy/APAP)  N=513 (ITT analysis) | 4 months  Patients ≥ 40 years of age with moderate to severe OA pain of the hip or knee for at least 3 months that was not adequately controlled by short- acting opioid therapy. | Costs for medications, healthcare visits, hospitalizations, emergency department visits, diagnostic tests and procedures, home health care services, and assistive devices.  Cost related to time lost from paid work and unpaid regular activities. | * Patients in the CRO group had greater OA-related healthcare costs compared to oxy/APAP group ($1,951 vs. $1,155), driven by prescription medication costs ($751 vs. $134) and home healthcare service costs ($595 vs. $467). * Patients in the CRO group has lower OA-related societal costs compared to oxy/APAP group ($7,379 vs. $7,528, p=0.33). * Patients in the CRO group has larger portion of patients who improved (62.2% vs. 45.9%, p<0.001) and gained 0.0105 QALYs compared to the oxy/APAP group (p=0.17). * The base-case incremental cost-effectiveness analysis from the HCS perspective showed that the incremental mean cost per patient was $796, and the difference in proportion of patients improved was 0.163. Therefore, CRO was more costly and more effective than oxy/APAP, with incremental cost-effectiveness ratio of $4,883 per patient improved. From the societal perspective, the incremental mean cost per patient was $149 less in the CRO group compared with the oxy/APAP group. Therefore, CRO was less costly and more effective than the oxy/APAP group. * For the base-case incremental cost-utility analysis illustrated from the HCS perspective, the incremental mean cost per patient was $796, and 0.0105 QALYs were gained in the CRO group compared to the oxy/APAP group. Therefore, CRO was more costly and more effective than oxy/APAP, with an incremental cost-utility ratio of $75,810 per QALY gained. From the societal perspective, the incremental mean cost per patient was $149 less in the oxycodone group compared with the oxy/APAP group. Since oxycodone was less costly and more effective than oxy/APAP, an incremental cost-utility ratio was not calculated. |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Study Design and Treatments Compared** | **Time Horizon and Demographics** | **Model Inputs and Data Sources** | **Results: Base Case, Sensitivity Analysis and Limitations** |
| Berger A, Hoffman DL, Goodman S, et al. Therapy switching in patients receiving long-acting opioids. *Ann Pharmacother*.  2004;38(3): 389-  395. | Retrospective study  CR oxycodone (n=1,931), transdermal fentanyl (n=668), or CR morphine sulfate (n=449) compared in patients who switch long-acting opioid therapy vs. patients who do not switch therapy. | Patients who began therapy with CR oxycodone, transdermal fentanyl, and CR morphine sulfate, respectively between Jul 1,  1998 and Dec 31,  1999. | Analysis of Protocare Sciences Managed Care Database.  Time to switching was assessed in terms of the number of days between the index date and the date of first receipt of another long- acting opioid.  Attention was focused on the first therapy switch only.  Estimates of time switch and the cumulative percentage of patients switching in the 3 groups were generated using Kaplan– Meier techniques.  To compare the charges of patients who switched therapy versus those who did not, patients were pooled across the three treatment groups and restratified according to whether they switched therapy during follow-up. | * Among patients without cancer, the median time to switching was 63 days for CR oxycodone, 57 days for transdermal fentanyl, and 44 days for CR morphine sulfate. * Among patients with cancer, the median time to switching was 77 days for CR oxycodone, 52 days for transdermal fentanyl, and 26 days for CR morphine sulfate. * Among patients without cancer (n=2397), 341 (14.2%) switched long-acting opioid therapy during follow-up. Those who switched therapy were more likely to be women and to have low back pain and other spinal pain. Adjusted mean total healthcare charges during follow up were $9,666 higher among those who switched therapy compared with those who did not. Inpatient care accounted for 59.1% of the total charges among patients who switched therapy and 54.5% among those who did not. Charges for pain-related pharmacotherapy were greater among patients who switched long-acting opioid therapy compared with those who did not. * Among the 651 patients with cancer, 25.5% switched therapy during follow-up. Patients who switched therapy were more likely to have other spinal pain compared with those who did not switch. Adjusted mean total healthcare charges during follow-up were $18,641 higher among those who switched therapy compared with those who did not. Inpatient care accounted for 48.2% of total charges among patients who switched therapy and 42.2% among those who did not. Charges for pain-related pharmacotherapy were also greater among patients who switched long-acting opioid therapy. * Patients beginning treatment with CR oxycodone or transdermal fentanyl are less likely to switch therapy than those treated initially with CR morphine sulfate. Among patients with cancer, those receiving CR oxycodone or transdermal fentanyl were approximately 25% less likely to switch therapy, although this result did not achieve statistical significance. Patients who switch long-acting opioid therapy have significantly higher healthcare charges than those who do not. This finding persists after adjustment for covariates such as age, preexisting diagnoses, and pretreatment healthcare charges. Charges for inpatient and outpatient care, as well as for pain-related medications, were significantly higher for cancer and noncancer patients who switched therapy. |

AE=adverse event; ARR=absolute risk reduction; CR=controlled-release; ED=emergency department; ER=extended-release; HCS=healthcare system; ITT=intent-to-treat; OA=osteoarthritis; QALY= quality-adjusted-life-years; TACE= transarterial chemoembolization

**6. SUPPORTING INFORMATION**

## 6.1. References Contained in Dossier

#### Bibliography of OxyContin Clinical and Economic Studies:

Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig*. 2010;30(8):489-505.

Bartelson BB, Severtson S, Davis J, et al. A comparison of the street price of original and reformulated OxyContin and immediate release (IR) oxycodone products [poster]. Presented at: 14th World Congress on Pain of the International Association for the Study of Pain; August 27-31, 2012, Milan, Italy. Abstract # PF 085

Ben-Joseph R, Chen CC, De AP, Wade RL, Shah D. Consequences of patient access restriction to branded oxycodone hydrochloride extended-release tablets on healthcare utilization and costs in US health plans. *J Med Econ.* 2014; 17:708-718.

Bercovitch M, Adunsky A. High dose controlled-release oxycodone in hospice care. *J Pain Palliat Care Pharmacother*. 2006;20(4):33-39.

Berger A, Hoffman DL, Goodman S, et al. Therapy switching in patients receiving long-acting opioids. *Ann Pharmacother*. 2004;38(3):389-395.

Binsfeld H, Szczepanski L, Waechter S, Richarz U, Sabatowski R. A randomized study to demonstrate noninferiority of once-daily OROS hydromorphone with twice-daily sustained release oxycodone for moderate to severe chronic noncancer pain. *Pain Pract*. 2010;10:404-415.

Black RA, Coplan P, Cassidy TA, Chilcoat H, Budman SH, Landau C, Butler SF. Effects of reformulated OxyContin® among patients assessed for substance abuse treatment in the NAVIPPRO sentinel surveillance network [poster]. Presented at: 31st Annual Meeting of the American Pain Society; May 16-19, 2012, Honolulu, HI.

Bruera E, Belzile M, Pituskin E, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J Clin Oncol.* 1998;16(10):3222-3229.

Butler SF, Cassidy TA, Chilcoat H, et al. Abuse rates and routes of administration of reformulated extended- release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *J Pain*. 2013;14(4):351-358. <http://dx.doi.org/10.1016/j.jpain.2012.08.008>.

Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol.* 1999;26(4):862-869.

Cassidy TA, Coplan P, Black RA, Chilcoat H, Budman SH, Butler SF. Change in routes of administration for OxyContin and comparators following introduction of reformulated OxyContin among individuals assessed for substance abuse [poster]. Presented at: 74th Annual Scientific Meeting of the College on Problems of Drug Dependence; June 9-14, 2012, Palm Springs, CA. Abstract #88.

Cheville A, Chen A, Oster G, et al. A randomized trial of controlled-release oxycodone during inpatient rehabilitation following unilateral total knee arthroplasty. *J Bone Joint Surg Am.* 2001;83-A(4):572-576.

Chilcoat H, Bartelson BB, Coplan P, et al. Difference in rates of abuse following reformulation of extended- release oxycodone using data from the RADARS® system poison center program [Poster]. Presented at: American Academy of Physical Medicine and Rehabilitation’s 2012 Annual Assembly; Nov 15-18, 2012, Atlanta, GA. Abstract # 99 at: [http://ac.els-cdn.com/S1934148212011914/1-s2.0-S1934148212011914-](http://ac.els-cdn.com/S1934148212011914/1-s2.0-S1934148212011914-main.pdf?_tid=421c85ce-7b8e-11e2-9bd700000aab0f01&amp;acdnat=1361386350_f5cd6cc1c823f61fd0667b076dc34695)  [main.pdf?\_tid=421c85ce-7b8e-11e2-9bd700000aab0f01&acdnat=1361386350\_f5cd6cc1c823f61fd0667b076](http://ac.els-cdn.com/S1934148212011914/1-s2.0-S1934148212011914-main.pdf?_tid=421c85ce-7b8e-11e2-9bd700000aab0f01&amp;acdnat=1361386350_f5cd6cc1c823f61fd0667b076dc34695)  [dc34695](http://ac.els-cdn.com/S1934148212011914/1-s2.0-S1934148212011914-main.pdf?_tid=421c85ce-7b8e-11e2-9bd700000aab0f01&amp;acdnat=1361386350_f5cd6cc1c823f61fd0667b076dc34695). Accessed 04/2015.

Chilcoat H, Bartelson BB, Coplan P, et al. Changes in diversion rates following the introduction of a reformulated extended-release oxycodone product. [Poster]. Presented at: American Academy of Physical Medicine and Rehabilitation’s 2012 Annual Assembly; Nov 15-18, 2012, Atlanta, GA. Abstract # 282 at: [http://ac.els-cdn.com/S1934148212013627/1-s2.0-S1934148212013627-main.pdf?\_tid=b500b372-7b8d-11e2-](http://ac.els-cdn.com/S1934148212013627/1-s2.0-S1934148212013627-main.pdf?_tid=b500b372-7b8d-11e2-9bd7-00000aab0f01&amp;acdnat=1361386113_428d920656536d0c4b5d4dd26951bd23)  [9bd7-00000aab0f01&acdnat=1361386113\_428d920656536d0c4b5d4dd26951bd23](http://ac.els-cdn.com/S1934148212013627/1-s2.0-S1934148212013627-main.pdf?_tid=b500b372-7b8d-11e2-9bd7-00000aab0f01&amp;acdnat=1361386113_428d920656536d0c4b5d4dd26951bd23). Accessed 04/2015.

Chilcoat H, Coplan P, Cassidy TA, Black RA, Landau C, Budman SH, Butler SF. Impact of reformulated OxyContin on rates of abuse through oral and non-oral routes among individuals assessed in substance abuse treatment [poster]. Presented at: 74th Annual Scientific Meeting of the College on Problems of Drug Dependence; June 9-14, 2012, Palm Springs, CA. Abstract #103.

Chilcoat H, Coplan P, Sessler N, et al. Impact of an Opioid Reformulation with Abuse-Deterrent Properties on Doctor-Shopping. Presented at the American Pain Society 33rd Annual Scientific Meeting, April 30-May 3, 2014, Tampa, FL.

Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. *NEJM*. 2012;367:187-189.

Citron ML, Kaplan R, Parris WCV, et al. Long-term administration of controlled-release oxycodone tablets for the treatment of cancer pain. *Cancer Invest.* 1998;16(8):562-571.

Cone EJ, Giordano J, Weingarten B. Laboratory based in vitro tamper testing on reformulated OxyContin: An iterative and incremental scientific approach [poster]. Presented at: 74th Annual Scientific Meeting of the College on Problems of Drug Dependence; June 9-14, 2012, Palm Springs, CA. Abstract #115.

Cone EJ, Giordano J, Weingarten B. An iterative model for in vitro laboratory assessment of tamper deterrent formulations. *Drug Alcohol Depend*. 2013; 131:100-105. <http://dx.doi.org/10.1016/j.drugalcdep.2012.12.006>.

Coplan P, Kale H, Sandstrom L, Chilcoat H. Effects of Reformulated OxyContin® on Opioid Abuse in the National Poison Data System [poster]. Presented at: 31st Annual Meeting of the American Pain Society; May 16-19, 2012, Honolulu, HI.

Coplan P, Kale H, Sandstrom L, Chilcoat H. Changes after reformulation of extended-release oxycodone in calls to poison centers for oxycodone and heroin [poster]. Presented at: 14th World Congress on Pain of the International Association for the Study of Pain; August 27-31, 2012, Milan, Italy. Abstract #PF012.

Coplan PM, Kale H, Sandstrom L, Landau C, Chilcoat HW. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. Pharmacoepidemiol Drug Saf. 2013;22(12): 1274-1282. <http://dx.doi.org/10.1002/pds.3522>.

Data on File. Stamford, CT: Purdue Pharma LP.

Data on File [OTR3001]. Stamford, CT: Purdue Pharma L.P.

de Beer J , Winemaker MJ , Donnelly GAE , et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. *Can J Surg.* 2005;48(4):277-283.

DeVeaugh-Geiss A, Leukefeld C, Havens J, Coplan P, Chilcoat H. Routes of administration and frequency of abuse of OxyContin and immediate-release oxycodone in a rural Kentucky county following introduction of reformulated OxyContin [poster]. Presented at: 74th Annual Scientific Meeting of the College on Problems of Drug Dependence; June 9-14, 2012, Palm Springs, CA. Abstract #146.

Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain*. 2009;142(3):209-217.

Ferrares F, Becchimanzi G, Bernardo M, et al. Pain treatment with high-dose, controlled-release oxycodone: an Italian perspective. *Ther Clin Risk Manag*. 2008;4(4):665-671.

Gatti A, Longo G, Sabato E, Sabato AF. Long-term controlled-release oxycodone and pregabalin in the treatment of non-cancer pain: an observational study. *Eur Neurol*. 2011;65(6):317-322.

Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology.* 2003;60(6):927-934.

Ginsberg B, Sinatra RS, Adler LJ, et al. Conversion to oral controlled-release oxycodone from intravenous opioid analgesic in the postoperative setting. *Pain Med.* 2003;4(1):31-38.

Giuggioli D, Manfredi A, Colaci M, Ferri C. Oxycodone in the long-term treatment of chronic pain related to scleroderma skin ulcers. *Pain Med*. 2010;11(10):1500-1503.

Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain.* 1999;15(3): 179-183.

Harris SC, Perrino PJ, Colucci SV, Mandarino DA. Effects of various tampering methods on exposure to oxycodone in healthy subjects [poster]. Presented at: 74th Annual Scientific Meeting of the College on Problems of Drug Dependence; June 9-14, 2012, Palm Springs, CA. Abstract #242.

Harris SC, Perrino PJ, Smith I, et al. Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users. J Clin Pharmacol. 2014;54(4):468-477. <http://dx.doi.org/10.1002/jcph.235>.

Hartung DM, Middleton L, Haxby DG, et al. Rates of adverse events of long-acting opioids in a state medicaid program. *Ann Pharmacother*. 2007;41(6):921-928. Erratum in: *Ann Pharmacother*. 2007 Sep;41(9):1552.

Havens JR, Leukefeld CG, DeVeaugh-Geiss AM, Coplan P, Chilcoat HD. The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers. *Drug Alcohol Depend*. 2014;139:9-17. <http://dx.doi.org/10.1016/j.drugalcdep.2014.02.018>.

Illgen RL. Pellino TA, Gordon DB, et al. Prospective analysis of a novel long-acting oral opioid analgesic regimen for pain control after total hip and knee arthroplasty*. J Arthroplasty.* 2006. 21(6):814-820.

Kampe S, Warm M, Kaufmann J, et al. Clinical efficacy of controlled-release oxycodone 20mg administered on a 12-h dosing schedule on the management of postoperative pain after breast surgery for cancer. *Curr Med Res Opin.* 2004;20(2): 199-202.

Kampe S, Wolter K, Warm M, Dagtekin O, Shaheen S, Landwehr S. Clinical equivalence of controlled-release oxycodone 20 mg and controlled-release tramadol 200 mg after surgery for breast cancer. *Pharmacology*.

2009;84(5):276-281.

Kaplan R, Parris WCV, Citron ML, et al. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *J Clin Oncol*. 1998;16(10):3230-3237.

Kirson NY, Shei A, White AG, Birnbaum HG, Ben-Joseph R, Rossiter LF, Michna E. Societal Economic Benefits Associated with an Extended-Release Opioid with Abuse-Deterrent Technology in the U.S. Pain Medicine. 2014; 15(9):1450-1454. <http://dx.doi.org/10.1111/pme.12489>.

Leukefeld CG, Buer LM, Young A, et al. Changes in prescription and OxyContin drug abuse patterns in rural Kentucky county. Presented at: 74th Annual Scientific Meeting of the College on Problems of Drug Dependence; June 9-14, 2012, Palm Springs, CA. Abstract #358.

Li X-M, Liu D-Q,Wu H-Y,Yang C, Yang L. Controlled-release oxycodone alone or combined with gabapentin for management of malignant neuropathic pain. *Chin J Cancer Res*. 2010;22(1):80-86.

Markenson JA, Croft J, Zhang PG, Richards P. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clin J Pain*. 2005;21(6):524-535.

Marshall DA, Strauss ME, Pericak D, et al. Economic evaluation of controlled-release oxycodone vs oxycodone-acetaminophen for osteoarthritis pain of the hip or knee. *Am J Manag Care*. 2006;12(4):205-214.

McNaughton EC, Coplan P, Black RA, Weber S, Chilcoat H, Butler SF. Monitoring of internet forums to evaluate reactions to the introduction of reformulated OxyContin to deter abuse. *J Med Internet Res*.

2014;16(5):e119. <http://www.jmir.org/2014/5/e119/>.

Mercadante S, Ferrera P, David F, Casuccio A. The use of high doses of oxycodone in an acute palliative care unit. *Am J Hosp Palliat Care*. 2011;28:242-244.

Michna E, Kirson NY, Shei A, Birnbaum HG, Ben-Joseph R. Use of prescription opioids with abuse-deterrent technology to address opioid abuse. Curr Med Res and Opin. 2014; 30(8): 1589-1598.

Mucci-LoRusso P, Berman BS, Silberstein PT, et al. Controlled-release oxycodone compared with controlled- release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *Eur J Pain*. 1998;2(3):239-249.

Parris WC-V, Johnson BW, Croghan MK, Moore MR, Khojasteh A, Reder RF, Kaiko RF, Buckley BJ. The use of controlled-release oxycodone for the treatment of chronic cancer pain: A randomized, double blind study. *J Pain Symptom Manage*.1998;16(4):205-211.

Perrino PJ, Colucci SV, Apseloff G, Harris SC. Pharmacokinetics, tolerability, and safety of intranasal administration of reformulated OxyContin tablets compared with original OxyContin tablets in healthy adults. *Clin Drug Investig*. 2013;33(6):441-449. Available at: <http://rd.springer.com/article/10.1007/s40261-013-0085-x>.

Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain*. 2007;23(4):287-299.

Ravera E, Di Santo S, Bosco R, Arboscello C, Chiarlone R. Controlled-release oxycodone tablets after transdermal-based opioid therapy in patients with cancer and non-cancer pain. *Aging Clin Exp Res*. 2011;23(5- 6):328-332.

Richarz U, Waechter S, Sabatowski R, Szczepanski L, Binsfeld H. Sustained safety and efficacy of once-daily hydromorphone extended-release (OROS® hydromorphone ER) compared with twice-daily oxycodone controlled-release over 52 weeks in patients with moderate to severe chronic noncancer pain. *Pain Pract*. 2013 Jan;13(1):30-40.

Ried CM, Martin RM, Sterne JA, et al. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166(21):837-843.

Riley J, Eisenberg E, Muller-Schwefe G, et al. Oxycodone: a review of its use in the management of pain. *Curr Med Res Opin*. 2008;24(1):175-192.

Rischitelli DG, Karbowicz SH. Safety and efficacy of controlled-release oxycodone: a systematic literature review. *Pharmacotherapy*. 2002;22(7):989-904.

Rossiter LF, Kirson NY, Shei A, et al. Medical Cost Savings Associated with an Extended-Release Opioid with Abuse-Deterrent Technology in the U.S. J Med Econ. 2014; 17(4):279-287. <http://informahealthcare.com/doi/pdf/10.3111/13696998.2014.897628>

Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: Placebo-controlled trial and long-term evaluation. *Arch Intern Med*. 2000;160(6): 853-860.

Rothwell MP, Pearson D, Hunter JD, et al. Oral oxycodone offers equivalent analgesia to intravenous patient- controlled analgesia after total hip replacement: a randomized, single-centre, non-blinded, non-inferiority study. *Br J Anaesth*. 2011;106(6):865-872.

Sellers EM, Perrino PJ, Colucci SV, Harris SC. Attractiveness of reformulated OxyContin tablets: assessing comparative preferences and tampering potential. *J Psychopharmacol*. 2013;27(9):808-816. Available at: <http://jop.sagepub.com/content/early/2013/06/17/0269881113493364>.

Sessler NE, Baumgartner TF, Coplan PM. Changes in number of spontaneous adverse event reports of drug abuse, intentional drug misuse, medication error, and overdose after reformulation of OxyContin. Presented at PainWeek 2012; September 5-8, 2012, Las Vegas, NV. Abstract # 100. Available at: <http://www.painweek.org/media/mediafile_attachments/02/572-painweek2012abstracts.pdf>. Accessed 09/2013.

Sessler NE, Downing JM, Kale H, Harding B, Baumgartner TF, Coplan PM. Effects of reformulating extended- release oxycodone on fatal adverse event reports. Presented at PainWeek 2012; September 5-8, 2012, Las Vegas, NV. Abstract # 101 Available at: [http://www.painweek.org/media/mediafile\_attachments/02/572-](http://www.painweek.org/media/mediafile_attachments/02/572-painweek2012abstracts.pdf.%20Accessed%2009/2013)  [painweek2012abstracts.pdf. Accessed 09/2013](http://www.painweek.org/media/mediafile_attachments/02/572-painweek2012abstracts.pdf.%20Accessed%2009/2013).

Sessler NE, Downing JM, Kale H, Chilcoat HD, Baumgartner TF, Coplan PM. Reductions in reported deaths following introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation.

Pharmacoepidemiol Drug Saf. 2014;23(12):1238-1246. <http://onlinelibrary.wiley.com/doi/10.1002/pds.3658/full>

Severtson SG, Bartelson BB, Davis JM, et al. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. *J Pain*. 2013; 14(10):1122-1130. <http://dx.doi.org/10.1016/j.jpain.2013.04.011>.

Stambaugh JE, Reder RF, Stambaugh MD, et al. Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate- release oral oxycodone in cancer pain patients. *J Clin Pharmacol.* 2001;41(5):500-506.

Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology.* 1998;50(6):1837-1841.

Watson CPN, Moulin D, WW J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain*. 2003;105(1-2):71-78.

Wild EJ, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Practice*. 2010;10(5):416-427.

Wirz S, Wartenberg H, Wittmann M, Nadstawek J. Post-operative pain therapy with controlled-release oxycodone or controlled release tramadol following orthopedic surgery: A prospective, randomized, double- blind investigation. *The Pain Clinic*. 2005;17(4):367-376.

Yao P, Meng LX, Ma JM, et al. Sustained-release oxycodone tablets for moderate to severe painful diabetic peripheral neuropathy: A multicenter, open-labeled, postmarketing clinical observation. *Pain Med*.

2012;13(1):107-114.

Zhou B, Wang J, Yan Z, Shi P, Kan Z. Liver cancer: effects, safety, and cost-effectiveness of controlled- release oxycodone for pain control after TACE. *Radiology*. 2012 Mar;262(3):1014-21.

#### Additional References

ABC News, USA Today, Stanford University Medical Center. Broad experience with pain sparks a search for relief. Available at: <http://abcnews.go.com/images/Politics/979a1TheFightAgainstPain.pdf>. Accessed: 04/2015.

American Academy of Pain Medicine (AAPM) and the American Pain Society (APS). The use of opioids for the treatment of chronic pain. (Consensus Statement). *Clin J Pain*. 1997;13:6-8.

American College of Occupational and Environmental Medicine (ACOEM). ACOEM guidelines for the chronic use of opioids. Elk Grove Village, IL: American College of Occupational and Environmental Medicine. 2011.

American Geriatric Society (AGS) Panel Persistent Pain in Older Persons. The management of persistent pain in older persons. *J Am Geriatr Soc*. 2002;50(Suppl 6):S205-S224.

American Geriatric Society (AGS) Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*.

2009;57(8):1331-1346.

American Liver Foundation - Know your dose [webpage]. American Liver Foundation. 2014; Available at: <http://www.liverfoundation.org/education/knowyourdose>. Accessed 04/2015.

American Pain Foundation (APF). An overview of American pain surveys. *J Pain Palliat Pharmacother*. 2007;21(4):59-67.

American Pain Society (APS). *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. 6th ed. Glenview, IL: American Pain Society; 2008.

American Society of Anesthesiologists. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology.* 2010;810-833.

Argoff CE, Backonja MM, Belgrade MJ, et al. Consensus guidelines: assessment, diagnosis, and treatment of diabetic peripheral neuropathic pain. *Mayo Clin Proc*. 2006; 81(4):S12-S25.

Arnow BA, Hunkeler EM, Blasey CM, et al. Comorbid depression, chronic pain, and disability in primary care.

*Psychosom Med*. Mar-Apr 2006;68(2):262-268.

Avinza (morphine sulfate capsule, extended release) Prescribing Information. New York, NY: Pfizer Laboratories Div Pfizer Inc; 2014.

Baser O, Xie L, Mardekian J, Schaaf D, Wang L, Joshi AV. Prevalence of Diagnosed Opioid Abuse and its Economic Burden in the Veterans Health Administration. *Pain Practice*. 2014;14(5):437-445.

Baumann TJ and Strickland J. Pain management. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw-Hill; 2008: Chapter 62.

Benziger DP, Levy SA, Fitzmartin RD, Reder R. Dose proportionality of 10, 20, and 40 mg controlled-release oxycodone hydrochloride tablets (OxyContin) [abstract 188]. Pharmacotherapy. 1995; 15(3):391.

Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal Costs of Prescription Opioid Abuse, Dependence, and Misuse in the United States. *Pain Med.* 2011;12(4):657-667.

Briggs A, Scott E, Steele K. Impact of osteoarthritis and analgesic treatment on quality of life of an elderly population. *Ann Pharmacother*. 1999;33(11):1154-1159.

Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy.

*Neurology*. 2011;76:1758–1765.

Budnitz DS, Lovegrove MC, Crosby AE. Emergency department visits for overdoses of acetaminophen- containing products. *Am J Prev Med.* Jun 2011;40(6):585-592.

Butrans (buprenorphine) Transdermal System Prescribing Information. Stamford, CT: Purdue Pharma LP; 2014.

Center for Medicare and Medicaid Services. Medicare part D overutilization monitoring system. Baltimore, MD: Center for Medicare and Medicaid Services; 2014

Cherny NI. Opioid analgesics: comparative features and prescribing guidelines*. Drugs*. 1996;51:713-37.

Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007;147(7):478- 491.

Chou R, Fanciullo GJ, Fine PG, et al. Opioid treatment guidelines: clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.

Chou R. In the Clinic: Low Back Pain. *Ann Intern Med*. 2014;160(11):ITC6-1-ITC6-16.

Curhan SG, Eavey R, Shargorodsky J, Curhan GC. Analgesic use and the risk of hearing loss in men. *Am J Med.* 2010;123(3):231-237.

Curhan SG, Shargorodsky J, Eavey R, Curhan GC. Analgesic use and the risk of hearing loss in women. *Am J Epidemiol.* 2012;176(6):544-554.

Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. *Psychosom Med.* Sep-Oct 2002;64(5):773-786.

Dolophine (methadone hydrochloride) tablets Prescribing Information. Columbus OH: Roxane Laboratories, Inc; 2014.

Dubinsky RM, Kabbani H, El-Chami Z, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;3(6):959-965.

Duragesic (Fentanyl Transdermal System) Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2014.

Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis.* 2007;44(Suppl 1):S1-26.

Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85(3 Suppl):S3-14.

Embeda (morphine sulfate and naltrexone hydrochloride) extended -release capsules Presecribing Information. New York, NY: Pfizer Laboratories Div Pfizer Inc.; 2014

Exalgo (hydromorphone HCl) extended release tablets Prescribing Information. Hazelwood, MO: Mallinckrodt, Inc; 2014.

Food and Drug Administration. Guidance for industry: abuse-deterrent opioids--evaluation and labeling. Rockville, MD: Food and Drug Administration; April 2015. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>. Accessed 04/ 2015.

Food and Drug Administration. Improving prescription container labels for acetaminophen-containing medicines. 2014; Available at: [http://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/ucm188762.htm#acetaminophen.](http://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/ucm188762.htm#acetaminophen) Accessed Nov 2014.

Galer BS, Gianas A, Jensen MP. Painful diabetic neuropathy: epidemiology, pain description, and quality of life. *Diabetes Res Clin Pract.* 2000;47(2):123-128.

Gourlay GK. Advances in opioid pharmacology. *Support Care Cancer*. 2005;13:153-9.

Heiskanen T and Kalso E. Controlled-release oxycodone and morphine in cancer related pain. *Pain*. 1997; 73:37-45.

Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64(4):465-74.

Hooten W, Timming R, Belgrade M, et al. Assessment and management of chronic pain. Bloomington, MN: Institute for Clinical Systems Improvement; 2013.

Institute of Medicine (IOM). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: The National Academies Press. 2011.

Inturrisi CE. Clinical pharmacology of opioids for pain*. Clin J Pain.* 2002;18(Suppl 4):S3-13.

Hysingla ER (hydrocodone bitartrate) extended-release tablets Prescribing Information. Stamford CT: Purdue Pharma LP; 2014.

Kadian (morphine sulfate) extended-release capsule Prescribing Information. Parsippany, NJ: Actavis Kadian LLC; 2014.

Langer R. Polymer-controlled drug delivery systems. *Acc Chem Res*. 1993;26:537-542.

Leider HL, Dhaliwal J, Davis EJ, Kulakodlu M, Buikema AR. Healthcare costs and nonadherence among chronic opioid users*. Am J Manag Care.* Jan 2011;17(1):32-40.

Li C, Martin BC. Trends in emergency department visits attributable to acetaminophen overdoses in the United States: 1993-2007. *Pharmacoepidemiol Drug Saf*. Aug 2011;20(8):810-818.

Loeser J, Arendt-Nielsen L, Baron R, et al. Pain terms: a current list with definitions and notes on usage. Classification of chronic pain. 2, revised ed. Washington, DC: International Association for the Study of Pain; 2011.

Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) Guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I – evidence assessment. *Pain Physician*. 2012;15:S1-S66

Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP): Guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2 - guidance. *Pain Physician.* 2012;15:S67- S116.

Manthripragada AD, Zhou EH, Budnitz DS, Lovegrove MC, Willy ME. Characterization of acetaminophen overdose-related emergency department visits and hospitalizations in the United States. *Pharmacoepidemiol Drug Saf.* Aug 2011;20(8):819-826.

McAdam-Marx C, Roland CL, Cleveland J, Oderda GM. Costs of opioid abuse and misuse determined from a Medicaid database. *J Pain Palliat Care Pharmacother*. 2010;24(1):5-18.

McCarberg BH, Nicholson BD, Todd KH, Palmer T, Penles L. The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an Internet survey. *Am J Ther*. 2008;15(4):312-320.

McGill MR, Jaeschke H. Metabolism and disposition of acetaminophen: recent advances in relation to hepatotoxicity and diagnosis. *Pharm Res.* Sep 2013;30(9):2174-2187.

Michna E, Duh MS, Korves C, Dahl JL. Removal of opioid/acetaminophen combination prescription pain medications: assessing the evidence for hepatotoxicity and consequences of removal of these medications. *Pain Med.* Mar 2010;11(3):369-378.

MS Contin (morphine sulfate extended-release tablets) Prescribing Information. Stamford CT: Purdue Pharma LP; 2014.

National Center for Health Statistics (NCHS). Health, United States, 2011: With Special Feature on Socioeconomic Status and Health. Hyattsville, MD. 2012.

National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic non- cancer pain. Version 5.6. April 2010. Available at: <http://nationalpaincentre.mcmaster.ca/opioid/>. Accessed 04/2015.

Nucynta ER (tapentadol hydrochloride tablet, film coated, extended release) Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2014.

Opana ER (oxymorphone hydrochloride tablet, extended release) Prescribing Information. Malvern, PA: Endo Pharmaceuticals Inc.; 2014.

Opioid Therapy Guideline Update Working Group. Veterans Health Administration/Department of Defense (VA/DoD) clinical practice guideline: management of opioid therapy for chronic pain. Washington, DC:

Veterans Health Administration, Department of Defense. 2010 May. Available at: <http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf>. Accessed 04/2015.

OxyContin (oxycodone HCl extended-release tablet) Prescribing Information. Stamford, CT: Purdue Pharma LP; 2015.

Percocet® (oxycodone hydrochloride and acetaminophen) Prescribing Information. Chadds Ford, PA: Endo Pharmaceuticals Inc; 2013.

Pergolizzi J, Boger RH, Budd K, Dahan A, Erdine S, Hans G, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Practice*. 2008 Jul;8(4):287-313.

Porreca F, Schug SA, Bellamy N. Challenging Perceptions in Chronic Pain. 2006 (Mar 17). The Postgraduate Institute for Medicine. Available at: <http://www.medscape.org/viewarticle/521494>. Accessed 09/2013.

Portenoy RK. Current pharmacotherapy of chronic pain. *J Pain Symptom Manage*. 2000;19(Suppl 1):S16-S20.

Rasu RS, Vouthy K, Crowl AN, et al. Cost of pain medication to treat adult patients with nonmalignant chronic pain in the United States. *J Manag Care Pharm.* Sep 2014;20(9):921-928.

Reisine T, Pasternack G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, eds-in-chief. *Goodman and Gilman’s The Pharmacological Basis of Therapeutics*. 9th ed. New York:McGraw Hill; 1996:521- 555.

Rice B, Kirson N, Shei A, et al. Hidden costs to employers of opioid abuse--healthecare costs, work-loss costs, and prevalence of opioid abuse among comercially-insured beneficiaries [poster]. Presented at: PAINWeek 2013; Las Vegas, NV. Available at: [http://conference.painweek.org/media/mediafile\_attachments/00/650-](http://conference.painweek.org/media/mediafile_attachments/00/650-painweek2013acceptedabstracts.pdf.%20Accessed%20Nov%202014)  [painweek2013acceptedabstracts.pdf. Accessed Nov 2014](http://conference.painweek.org/media/mediafile_attachments/00/650-painweek2013acceptedabstracts.pdf.%20Accessed%20Nov%202014).

Rice JB, Kirson NY, Shei A, et al. Estimating the costs of opioid abuse and dependence from an employer perspective: a retrospective analysis using administrative claims data. *Applied Health Economics and Health policy*. Aug 2014;12(4):435-446.

Ricci JA, Stewart WF, Chee E, et al. Pain exacerbation as a major source of lost productive time in US workers with arthritis. *Arthritis Rheum*. 2005; 53(5):673-681.

Schiller JS, Lucas JW, Peregoy JA. Summary Health Statistics for the U.S. Population: National Health Interview Survey, 2011. National Center for Health Statistics. Vital Health Stat 10(255). 2012. Available from: <http://www.cdc.gov/nchs/data/series/sr_10/sr10_256.pdf>. Accessed 04/2015.

Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharmaceutical Research*. 2000; 17(10):1278-1283.

Substance Abuse and Mental Health Services Administration. Drug abuse warning network, 2011: national estimates of drug-related emergency department visits. In: US Department of Health and Human Services, ed. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.

Substance Abuse and Mental Health Services Administration. Results from the 2012 national survey on drug use and health: summary of national findings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.

Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290(18):2443-2454.

Tsang A, Von Kroff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: Gender and age differences and comorbidity with depression-anxiety disorders. *J Pain*. 2008;9:883-891.

Tylenol (acetminophen tablets) Product Label. McNeil Consumer Healthcare; 2009.

Vicodin , Vicodin ES, Vicodin HP (hydrocodone bitartrate and acetaminophen) TABLETS, USP Prescribing Information. North Chicago, IL: AbbVie Inc; 2014.

Volkow ND, Li TK. Drug addiction: the neurobiology of behaviour gone awry. *Nat Rev Neurosci* Dec. 2004;5(12):963-970.

Von Korff M, Crane P, Lane M, et al. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. *Pain.* Feb 2005;113(3):331-339.

Weisberg MB, Clavel AL Jr. Why is chronic pain so difficult to treat? *Postgrad Med*. 1999;106(6):141-164.

White AG, Birnbaum HG, Mareva MN, et al. Direct costs of opioid abuse in an insured population in the United States. *J Manag Care Pharm.* Jul-Aug 2005;11(6):469-479.

Wisconsin Medical Society Task Force on Pain Management (WMS). Guidelines for the assessment and management of chronic pain. *WMJ*. 2004;103(3):15-42.

World Health Organization (WHO). *Cancer Pain Relief*. 2nd ed. Geneva: World Health Organization.1996.

Zydone (hydrocodone bitartrate and acetaminophen tablets, USP) Prescribing Information. Chadds Ford, PA: Endo Pharmaceuticals; 2011.

Zohydro ER (hydrocodone bitartrate) extended-release capsules Prescribing Information. Manufactured for Zogenix, Inc., San Diego, CA 92130 by Alkermes Gainesville LLC under license from Alkermes Pharma Ireland Limited (APIL), Ireland; 2015



## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use OXYCONTIN® safely and effectively. See full prescribing information for OXYCONTIN.**

**OXYCONTIN® (oxycodone hydrochloride) extended-release tablets, for oral use, CII Initial U.S. Approval: 1950**

**WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRA- TORY DEPRESSION; ACCIDENTAL INGES- TION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION**

***See full prescribing information for complete boxed warning.***

* **OXYCONTIN exposes users to risks of addictions, abuse and misuse,**

**which can lead to overdose and death. Assess each patient’s risk before prescribing and monitor regularly for development of these behaviors and conditions. (5.1)**

* **Serious, life-threatening, or fatal respi- ratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct pa- tients to swallow OXYCONTIN tablets whole to avoid exposure to a poten- tially fatal dose of oxycodone. (5.2)**
* **Accidental ingestion of OXYCONTIN, especially in children, can result in a fatal overdose of oxycodone. (5.2)**
* **Prolonged use of OXYCONTIN dur- ing pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not rec- ognized and treated. 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. (5.3)**

* **Initiation of CYP3A4 inhibitors (or dis- continuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone from OXYCONTIN. (5.14, 12.3)**

# ----RECENT MAJOR CHANGES---

Indications and Usage (1) 08/2015 Dosage and Administration (2) 08/2015

# ----INDICATIONS AND USAGE----

OXYCONTIN is an opioid agonist indicated for pain severe enough to require daily, around- the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

* 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.

Limitations of Use

* Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, reserve OXYCONTIN for use

in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inad- equate to provide sufficient management of pain. (1)

* OXYCONTIN is not indicated as an as- needed (prn) analgesic. (1)

# -DOSAGE AND ADMINISTRATION-

* To be prescribed only by health care provid- ers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
* Must swallow tablets intact. Do not cut, break, chew, crush, or dissolve tablets (risk of potentially fatal dose). (2.1, 5.1)
* Must take tablets one at a time, with enough water to ensure complete swallowing imme- diately after placing in mouth. (2.1, 5.9)
* OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
* Do not abruptly discontinue OXYCONTIN in a physically dependent patient. (2.9)

Adults: For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg tablets orally every 12 hours. See full prescribing information for instructions on conversion from opioids to OXY- CONTIN, titration and maintenance of therapy. (2.2, 2.3, 2.5)

Pediatric Patients 11 Years of Age and Older

* For use only in pediatric patients 11 years

and older already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days imme- diately preceding dosing with OXYCONTIN. (2.4)

* See full prescribing information for instruc- tions on conversion from opioids to OXYCON- TIN, titration and maintenance of therapy. (2.4, 2.5)

Geriatric Patients: In debilitated, opioid non- tolerant geriatric patients, initiate dosing at 1/3 to 1/2 the recommended starting dosage and titrate carefully. (2.7, 8.5)

Patients with Hepatic Impairment: Initiate dosing at 1/3 to 1/2 the recommended staring dosage and titrate carefully. (2.8, 8.6)

# DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 10 mg, 15 mg,

20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. (3)

# ------CONTRAINDICATIONS-------

* Significant respiratory depression. (4)
* Acute or severe bronchial asthma in an unmonitored setting or in absence of resus- citative equipment. (4)
* Known or suspected paralytic ileus and gastrointestinal obstruction. (4)
* Hypersensitivity to oxycodone. (4)

# -WARNINGS AND PRECAUTIONS-

* Risk of life-threatening respiratory depres- sion in elderly, cachectic, and debilitated patients, and in patients with chronic pul- monary disease: Monitor closely. (5.5, 5.6)
* Severe hypotension: Monitor during dosage initiation and titration. Avoid use of OXY- CONTIN in patients with circulatory shock. (5.7)
* Risk of use in patients with increased intra- cranial pressure, brain tumors, head injury, or impaired consciousness: Monitor for sedation and respiratory depression. Avoid use of OXYCONTIN in patients with impaired consciousness or coma. (5.8)
* Risk of obstruction in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction: Consider use of an alternative analgesic. (5.9)

# ------ADVERSE REACTIONS------

Most common adverse reactions (>5%) were constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. (6.1)

**To report SUSPECTED ADVERSE REAC-**

**TIONS, contact Purdue Pharma L.P. at**

**1-888-726-7535 or FDA at 1-800-FDA-1088**

**or** [***www.fda.gov/medwatch.***](http://www.fda.gov/medwatch)

# ------DRUG INTERACTIONS------

* + CNS depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, coma, and death. If decision to begin OXYCONTIN is made, start with 1/3 to 1/2 the recommended starting dosage and monitor closely. (2.6, 5.4, 7.1)
  + Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with

OXYCONTIN because they may reduce an- algesic effect of OXYCONTIN or precipitate withdrawal symptoms. (7.3)

# -USE IN SPECIFIC POPULATIONS-

* + Nursing mothers: Oxycodone has been detected in human milk. Closely monitor infants of nursing women receiving OXYCONTIN. (8.3)

**See 17 for PATIENT COUNSELING**

**INFORMATION and Medication Guide. Revised: 08/2015**

# FULL PRESCRIBING INFORMATION: CONTENTS\*

**WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRES- SION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION**

* + - 1. **INDICATIONS AND USAGE**
      2. **DOSAGE AND ADMINISTRATION**
         1. Important Dosage and Administra- tion Instructions
         2. Initial Dosage in Adults who are not Opioid Tolerant
         3. Conversion from Opioids to OXYCONTIN in Adults
         4. Initial Dosage in Pediatric Patients 11 Years and Older
         5. Titration and Maintenance of Therapy in Adults and Pediatric Patients 11 Years and Older
         6. Dosage Modifications with Concomi- tant Use of Central Nervous System Depressants
         7. Dosage Modifications in Geriatric Patients who are Debilitated and not Opioid-Tolerant
         8. Dosage Modifications in Patients with Hepatic Impairment
         9. Discontinuation of OXYCONTIN
      3. **DOSAGE FORMS AND STRENGTHS**
      4. **CONTRAINDICATIONS**
      5. **WARNINGS AND PRECAUTIONS**
         1. Addiction, Abuse, and Misuse
         2. Life-Threatening Respiratory Depression
         3. Neonatal Opioid Withdrawal Syndrome
         4. Interactions with Central Nervous System Depressants
         5. Use in Elderly, Cachectic, and Debilitated Patients
         6. Use in Patients with Chronic Pulmonary Disease
         7. Hypotensive Effects
         8. Use in Patients with Head Injury or Increased Intracranial Pressure
         9. Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen
         10. Use in Patients with Gastrointestinal Conditions
         11. Use in Patients with Convulsive or Seizure Disorders
         12. Avoidance of Withdrawal
         13. Driving and Operating Machinery
         14. Cytochrome P450 3A4 Inhibitors and Inducers
         15. Laboratory Monitoring
      6. **ADVERSE REACTIONS**
         1. Clinical Trial Experience
         2. Postmarketing Experience
      7. **DRUG INTERACTIONS**
         1. CNS Depressants
         2. Drugs Affecting Cytochrome P450 Isoenzymes
         3. Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics
         4. Muscle Relaxants
         5. Diuretics
         6. Anticholinergics
      8. **USE IN SPECIFIC POPULATIONS**
         1. Pregnancy
         2. Labor and Delivery
         3. Nursing Mothers
         4. Pediatric Use
         5. Geriatric Use
         6. Hepatic Impairment
         7. Renal Impairment
         8. Gender Differences
      9. **DRUG ABUSE AND DEPENDENCE**
         1. Controlled Substance
         2. Abuse
         3. Dependence
      10. **OVERDOSAGE**
      11. **DESCRIPTION**
      12. **CLINICAL PHARMACOLOGY**
          1. Mechanism of Action
          2. Pharmacodynamics
          3. Pharmacokinetics
      13. **NONCLINICAL TOXICOLOGY**
          1. Carcinogenesis, Mutagenesis, Impairment of Fertility
      14. **CLINICAL STUDIES**

1. **HOW SUPPLIED/STORAGE AND HANDLING**
2. **PATIENT COUNSELING INFORMATION**

\*Sections or subsections omitted from the full prescribing information are not listed

**FULL PRESCRIBING INFORMATION**

**WARNING: ADDICTION, ABUSE AND MIS- USE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYN- DROME; and CYTOCHROME P450 3A4 INTERACTION**

**Addiction, Abuse, and Misuse OXYCONTIN® exposes patients and other users to the risks of opioid addiction,**

**abuse and misuse, which can lead to over- dose and death. Assess each patient’s risk prior to prescribing OXYCONTIN**

**and monitor all patients regularly for the development of these behaviors or**

**conditions *[see Warnings and Precautions (5.1)].***

**Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respi- ratory depression may occur with use**

**of OXYCONTIN. Monitor for respiratory depression, especially during initiation of OXYCONTIN or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole; crushing, chewing, or dis- solving OXYCONTIN tablets can cause rap- id release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.2)].***

**Accidental Ingestion**

**Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.2)].***

**Neonatal Opioid Withdrawal Syndrome Prolonged use of OXYCONTIN 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 *[see Warn- ings and Precautions (5.3)].***

**Cytochrome P450 3A4 Interaction The concomitant use of OXYCONTIN**

**with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug ef- fects 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 and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.14) and Clinical Pharma- cology (12.3)].***

## INDICATIONS AND USAGE

OXYCONTIN is indicated for the manage- ment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

* 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.

Limitations of Use

* Because of the risks of addiction, abuse, and misuse with opioids, even at recom- mended doses, and because of the greater risks of overdose and death with extended- release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analge- sics or immediate-release opioids) are inef- fective, not tolerated, or would be otherwise inadequate to provide sufficient manage- ment of pain.
* OXYCONTIN is not indicated as an as-need- ed (prn) analgesic.

## DOSAGE AND ADMINISTRATION

**2.1 Important Dosage and Adminis- tration Instructions**

OXYCONTIN should be prescribed only by healthcare professionals who are knowl- edgeable in the use of potent opioids for the management of chronic pain.

* Initiate the dosing regimen for each patient individually, taking into account the patient’s prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)].*
* Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating OXYCONTIN therapy *[see Warnings and Precautions (5.2)].*
* Must take OXYCONTIN tablets whole, with enough water to ensure complete swallow- ing immediately after placing in the mouth.

Must take OXYCONTIN tablets one tablet at a time and must not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth *[see Warnings and Precautions*

*(5.9)].* Cutting, breaking, crushing, chewing, or dissolving OXYCONTIN tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death *[see Warnings and Precautions (5.1)].*

* OXYCONTIN 60 mg and 80 mg tablets, a sin- gle dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established.

## Initial Dosage in Adults who are not Opioid-Tolerant

The starting dosage for patients who are not opioid tolerant is OXYCONTIN 10 mg orally every 12 hours. Adult patients who are opioid

tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydro- morphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respi- ratory depression *[see Warnings and Precau- tions (5.2)].*

## Conversion from Opioids to OXYCONTIN in Adults

Conversion from Other Oral Oxycodone For-

mulations to OXYCONTIN

If switching from other oral oxycodone formu- lations to OXYCONTIN, administer one half of the patient’s total daily oral oxycodone dose as OXYCONTIN every 12 hours.

Conversion from Other Opioids to OXYCONTIN There are no established conversion ratios for conversion from other opioids to OXYCONTIN defined by clinical trials. Discontinue all other around-the-clock opioid drugs when OXYCON- TIN therapy is initiated and initiate dosing us- ing OXYCONTIN 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 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. Metha- done has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to OXYCONTIN

If switching from transdermal fentanyl patch to OXYCONTIN, ensure that the patch has been removed for at least 18 hours prior to starting OXYCONTIN. Although there has been no sys- tematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each

25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN, as there is limited documented experience with this conversion.

## 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 OXYCON- TIN, patients must be taking a minimum of 20 mg per day of oxycodone or its equivalent. OXYCONTIN is not appropriate for use in pedi-

atric patients requiring less than a 20 mg total

daily dose. Table 1, based on clinical trial ex- perience, displays the conversion factor when switching pediatric patients 11 years and older (under the conditions described above) from opioids to OXYCONTIN.

Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated. Although tables of oral and parenteral equiva- lents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and formulations.

As such, it is preferable to underestimate a patient’s 24-hour oral oxycodone requirements and provide rescue medication (e.g., immedi- ate-release opioid) than to overestimate the

24-hour oral oxycodone requirements and manage an adverse reaction.

Consider the following when using the infor- mation in Table 1.

* + - This is not a table of equianalgesic doses.
    - The conversion factors in this table are only for the conversion from one of the listed oral opioid analgesics to OXYCONTIN.
    - The table cannot be used to convert from OXYCONTIN to another opioid. Doing so will result in an over-estimation of the dose

of the new opioid and may result in fatal overdose.

* + - The formula for conversion from prior opi- oids, including oral oxycodone, to the daily dose of OXYCONTIN is mg per day of prior opioid x factor = mg per day of OXYCONTIN. Divide the calculated total daily dose by 2 to get the every-12-hour OXYCONTIN dose. If rounding is necessary, always round the dose down to the nearest OXYCONTIN tablet strength available.

## Table 1: Conversion Factors When Switching Pediatric Patients 11 Years and Older to OXYCONTIN

|  |  |
| --- | --- |
| **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.

Step #1: To calculate the estimated total OXYCONTIN daily dosage using Table 1:

* For pediatric patients taking a single opioid, sum the current total daily dosage of the opioid and then multiply the total daily dos- age by the approximate conversion factor to calculate the approximate OXYCONTIN 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 OXY- CONTIN 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 OXY- CONTIN tablet strength available and initiate OXYCONTIN therapy with that dose. If the calculated OXYCONTIN total daily dosage is less than 20 mg, there is no safe strength for conversion and do not initiate OXYCONTIN. Example conversion from a single opioid (e.g., hydrocodone) to OXYCONTIN: Using the conversion factor of 0.9 for oral hydro- codone in Table 1, a total daily hydrocodone dosage of 50 mg is converted to 45 mg of oxycodone per day or 22.5 mg of OXYCON-

TIN every 12 hours. After rounding down to the nearest strength available, the recom- mended OXYCONTIN starting dosage is 20 mg every 12 hours.

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. *[see Dosage and Ad- ministration (2.5)]* for important instructions on titration and maintenance of therapy.

There is limited experience with conversion from transdermal fentanyl to OXYCONTIN in pediatric patients 11 years and older. If

switching from transdermal fentanyl patch to OXYCONTIN, ensure that the patch has been removed for at least 18 hours prior to starting OXYCONTIN. Although there has been no sys- tematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN.

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

* 1. **Titration and Maintenance of Therapy in Adults and Pediatric Patients 11 Years and Older** Individually titrate OXYCONTIN to a dosage that provides adequate analgesia and minimizes ad- verse reactions. Continually reevaluate patients receiving OXYCONTIN to assess the mainte- nance of pain control, signs and symptoms

of opioid withdrawal, and adverse reactions, as well as monitoring for the development of addiction, abuse and misuse. Frequent com- munication is important among the prescriber, other members of the healthcare team, the

patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodi- cally reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dosage increase of OXYCON- TIN 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 OXY- CONTIN dosage. Because steady-state plasma concentrations are approximated in 1 day, OXYCONTIN dosage may be adjusted every 1 to 2 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.

## Dosage Modifications with Concomitant Use of Central Nervous System Depressants

If the patient is currently taking a central nervous system (CNS) depressant and the decision is made to begin OXYCONTIN, start with 1/3 to 1/2 the recommended starting dosage of OXYCONTIN and monitor patients for signs of respiratory depression, sedation, and hypotension *[see Warnings and Precautions (5.4), Drug Interactions (7.1)].*

## Dosage Modifications in Geriat- ric Patients who are Debilitated and not Opioid-Tolerant

For 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 *[see Use in Specific Populations (8.5)].*

## Dosage Modifications in Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at 1/3 to 1/2 the recommend- ed starting dosage followed by careful dosage titration *[see Clinical Pharmacology (12.3)].*

* 1. **Discontinuation of OXYCONTIN** When the patient no longer requires therapy with OXYCONTIN, gradually titrate the dosage downward to prevent signs and symptoms of withdrawal in the physically dependent patient. Do not abruptly discontinue OXYCONTIN.

## 3 DOSAGE FORMS AND STRENGTHS

* 10 mg film-coated extended-release tablets (round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other)
* 15 mg film-coated extended-release tablets (round, gray-colored, bi-convex tablets

debossed with OP on one side and 15 on the other)

* 20 mg film-coated extended-release tablets (round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other)
* 30 mg film-coated extended-release tablets (round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other)
* 40 mg film-coated extended-release tablets (round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other)
* 60 mg film-coated extended-release tablets (round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other)
* 80 mg film-coated extended-release tablets (round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other)

## CONTRAINDICATIONS

OXYCONTIN is contraindicated in patients with:

* Significant respiratory depression
* Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
* Known or suspected paralytic ileus and gastrointestinal obstruction
* Hypersensitivity (e.g., anaphylaxis) to oxy- codone *[see Adverse Reactions (6.2)]*

## WARNINGS AND PRECAUTIONS

* 1. **Addiction, Abuse, and Misuse** OXYCONTIN contains oxycodone, a Sched- ule II controlled substance. As an opioid, OXYCONTIN exposes users to the risks of ad- diction, abuse, and misuse *[see Drug Abuse and Dependence (9)].* As modified-release products such as OXYCONTIN deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present *[see Drug Abuse and Dependence (9)].*

Although the risk of addiction in any indi- vidual is unknown, it can occur in patients appropriately prescribed OXYCONTIN. Addic- tion can occur at recommended doses and if the drug is misused or abused.

Assess each patient’s risk for opioid addic- tion, abuse or misuse prior to prescribing OXYCONTIN, and monitor all patients receiv- ing OXYCONTIN for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient.

Patients at increased risk may be prescribed modified-release opioid formulations such as OXYCONTIN, but use in such patients neces- sitates intensive counseling about the risks and proper use of OXYCONTIN along with

intensive monitoring for signs of addiction, abuse, and misuse.

Abuse, or misuse of OXYCONTIN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death *[see Overdosage (10)].*

Opioid agonists are sought by drug abus- ers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OXYCONTIN. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)].* Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

## 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 *[see Overdosage (10)].* Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respira- tory depression can occur at any time during the use of OXYCONTIN, the risk is greatest during the initiation of therapy or following

a dose increase. Closely monitor patients for respiratory depression when initiating therapy with OXYCONTIN and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of OXYCONTIN are essential *[see Dosage and Administration (2)].* Overestimating the OXYCONTIN dose

when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

## Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during preg- nancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syn- drome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recog- nized and treated, and requires management according to protocols developed by neona- tology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid with-

drawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome pres- ents as irritability, hyperactivity and abnor- mal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

* 1. **Interactions with Central Nervous System Depressants** Hypotension and profound sedation, coma, or respiratory depression may result if OXYCON- TIN is used concomitantly with other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of OXYCONTIN in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient’s response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the

patient’s use of alcohol or illicit drugs that can cause CNS depression. If the decision to begin OXYCONTIN therapy is made, start with 1/3

to 1/2 the usual dose of OXYCONTIN, monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.1) and Dosage and Administra- tion (2.6)].*

## Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is

more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance com- pared to younger, healthier patients. Moni- tor such patients closely, particularly when initiating and titrating OXYCONTIN and when OXYCONTIN is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)].*

## Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic ob- structive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respi- ratory depression, particularly when initiating therapy and titrating with OXYCONTIN, as in these patients, even usual therapeutic doses of OXYCONTIN may decrease respiratory drive to the point of apnea *[see Warnings and Pre- cautions (5.2)].* Consider the use of alternative non-opioid analgesics in these patients if possible.

## Hypotensive Effects

OXYCONTIN 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 adminis- tration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7.1)].* Monitor these patients for signs of hypotension after initiating or titrating the dose of OXYCONTIN. In patients with circulatory shock, OXYCONTIN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OXYCONTIN in patients with circulatory shock.

* 1. **Use in Patients with Head Injury or Increased Intracranial Pressure** Monitor patients taking OXYCONTIN who

may be susceptible to the intracranial effects of 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 with OXYCONTIN. OXYCONTIN may reduce respiratory drive, and the resultant CO2 reten- tion can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of OXYCONTIN in patients with impaired consciousness or coma.

## Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

There have been post-marketing reports of

difficulty in swallowing OXYCONTIN tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or other- wise wet OXYCONTIN tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swal- lowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, and exac- erbation 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 gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

* 1. **Use in Patients with Gastrointestinal Conditions** OXYCONTIN is contraindicated in patients with GI obstruction, including paralytic ileus. The oxycodone in OXYCONTIN may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancre- atitis, for worsening symptoms. Opioids may cause increases in the serum amylase.

## Use in Patients with Convulsive or Seizure Disorders

The oxycodone in OXYCONTIN may aggravate

convulsions in patients with convulsive disor- ders, and may induce or aggravate seizures in some clinical settings. Monitor patients with

a history of seizure disorders for worsened seizure control during OXYCONTIN 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, including OXYCONTIN. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analge- sic effect and/or may precipitate withdrawal symptoms.

When discontinuing OXYCONTIN, gradually taper the dose *[see Dosage and Administration (2.9)].* Do not abruptly discontinue OXYCONTIN.

## Driving and Operating Machinery

OXYCONTIN may impair the mental or physical

abilities needed to perform potentially hazard- ous activities such as driving a car or operat- ing machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OXYCONTIN and know how they will react to the medication.

## Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major

role in the metabolism of OXYCONTIN, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations.

Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythro- mycin), azole-antifungal agents (e.g., ketocon- azole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid effects.

CYP450 inducers, such as rifampin, carba- mazepine, and phenytoin, 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 depen- dence to oxycodone.

If co-administration is necessary, caution is advised when initiating OXYCONTIN treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects

are achieved *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)].*

## Laboratory Monitoring

Not every urine drug test for “opioids” or “opi- ates” detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentra- tions below a specified “cut-off” value as “negative”. Therefore, if urine testing for oxycodone is considered in the clinical man- agement 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 REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

* Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
* Life-Threatening Respiratory Depression

*[see Warnings and Precautions (5.2)]*

* Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
* Interactions with Other CNS Depressants

*[see Warnings and Precautions (5.4)]*

* Hypotensive Effects *[see Warnings and Precautions (5.7)]*
* Gastrointestinal Effects *[see Warnings and Precautions (5.9, 5.10)]*
* Seizures *[see Warnings and Precautions (5.11)]*

## Clinical Trial Experience

Adult Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reac- tion rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may

not reflect the rates observed in practice. The safety of OXYCONTIN was evaluated in dou- ble-blind clinical trials involving 713 patients with moderate to severe pain of various eti- ologies. In open-label studies of cancer pain, 187 patients received OXYCONTIN in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approxi- mately 105 mg per day.

OXYCONTIN may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circula- tory depression, hypotension, or shock *[see Overdosage (10)].*

The most common adverse reactions (>5%) reported by patients in clinical trials compar- ing OXYCONTIN with placebo are shown in Table 2 below:

## TABLE 2: Common Adverse Reactions (>5%)

|  |  |  |
| --- | --- | --- |
| **Adverse Reaction** | **OXYCONTIN (n=227)** | **Placebo (n=45)** |
| **(%) (%)** | | |
| Constipation | (23) | (7) |
| Nausea | (23) | (11) |
| Somnolence | (23) | (4) |
| Dizziness | (13) | (9) |
| Pruritus | (13) | (2) |
| Vomiting | (12) | (7) |
| Headache | (7) | (7) |
| Dry Mouth | (6) | (2) |
| Asthenia | (6) | - |

Sweating (5) (2)

In clinical trials, the following adverse reac- tions were reported in patients treated with OXYCONTIN with an incidence between 1% and 5%:

**Gastrointestinal disorders:** abdominal pain, diarrhea, dyspepsia, gastritis

**General disorders and administration site conditions:** chills, fever

**Metabolism and nutrition disorders:**

anorexia

**Musculoskeletal and connective tissue disorders:** twitching

**Psychiatric disorders:** abnormal dreams, anxiety, confusion, dysphoria, euphoria, in- somnia, nervousness, thought abnormalities **Respiratory, thoracic and mediastinal disorders:** dyspnea, hiccups

**Skin and subcutaneous tissue disorders:**

rash

**Vascular disorders:** postural hypotension

The following adverse reactions occurred **in less than 1% of patients** involved in clinical trials:

**Blood and lymphatic system disorders:**

lymphadenopathy

**Ear and labyrinth disorders:** tinnitus

**Eye disorders:** abnormal vision **Gastrointestinal disorders:** dysphagia, eruc- tation, flatulence, gastrointestinal disorder, increased appetite, stomatitis

**General disorders and administration site conditions:** withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema **Injury, poisoning and procedural complica- tions:** accidental injury

**Investigations:** ST depression **Metabolism and nutrition disorders:** dehydration

**Nervous system disorders:** syncope, mi- graine, abnormal gait, amnesia, hyperkinesia, hypoesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perver- sion

**Psychiatric disorders:** depression, agitation, depersonalization, emotional lability, halluci- nation

**Renal and urinary disorders:** dysuria, hematuria, polyuria, urinary retention **Reproductive system and breast disorders:** impotence

**Respiratory, thoracic and mediastinal dis- orders:** cough increased, voice alteration **Skin and subcutaneous tissue disorders:** dry skin, exfoliative dermatitis

Clinical Trial Experience in Pediatric Patients 11 Years and Older

The safety of OXYCONTIN has been evalu- ated in one clinical trial with 140 patients 11 to 16 years of age. The median duration of treatment was approximately three weeks. The most frequently reported adverse events were vomiting, nausea, headache, pyrexia, and constipation.

Table 3 includes a summary of the incidence of treatment emergent adverse events re- ported in ≥5% of patients.

## Table 3: Incidence of Adverse Reac- tions Reported in 5.0% Patients 11 to 16 Years

|  |  |
| --- | --- |
| **System Organ Class Preferred Term** | **11 to 16 Years (N=140)**  **n (%)** |
| Any Adverse Event >= 5% | 71 (51) |
| GASTROINTESTINAL DISORDERS | 56 (40) |
| Vomiting | 30 (21) |
| Nausea | 21 (15) |
| Constipation | 13 (9) |
| Diarrhea | 8 (6) |
| GENERAL DISORDERS AND |  |
| ADMINISTRATION SITE |  |
| CONDITIONS | 32 (23) |
| Pyrexia | 15 (11) |
| METABOLISM AND NUTRITION |  |
| DISORDERS | 9 (6) |
| Decreased appetite | 7 (5) |
| NERVOUS SYSTEM DISORDERS | 37 (26) |
| Headache | 20 (14) |
| Dizziness | 12 (9) |
| SKIN AND SUBCUTANEOUS |  |
| TISSUE DISORDERS | 23 (16) |
| Pruritus | 8 (6) |

The following adverse reactions occurred in a clinical trial of OXYCONTIN in patients 11 to 16 years of age with an incidence between

≥1.0% and < 5.0%. Events are listed within each System/Organ Class.

**Blood and lymphatic system disorders:**

febrile neutropenia, neutropenia

**Cardiac disorders:** tachycardia **Gastrointestinal disorders:** abdominal pain, gastroesophageal reflux disease

**General disorders and administration site conditions:** fatigue, pain, chills, asthenia **Injury, poisoning, and procedural complica- tions:** procedural pain, seroma **Investigations:** oxygen saturation decreased, alanine aminotransferase increased, hemo- globin decreased, platelet count decreased, neutrophil count decreased, red blood cell count decreased, weight decreased **Metabolic and nutrition disorders:** hypo- chloremia, hyponatraemia

**Musculoskeletal and connective tissue disorders:** pain in extremity, musculoskeletal pain

**Nervous system disorders:** somnolence, hypoesthesia, lethargy, paresthesia **Psychiatric disorders:** insomnia, anxiety, depression, agitation

**Renal and urinary disorders:** dysuria, urinary retention

**Respiratory, thoracic, and mediastinal disorders:** oropharyngeal pain

**Skin and subcutaneous tissue disorders:**

hyperhidrosis, rash

* 1. **Postmarketing Experience** The following adverse reactions have been identified during post-approval use of con-

trolled-release oxycodone: abuse, addiction, aggression, amenorrhea, cholestasis, com- pleted suicide, death, dental caries, increased hepatic enzymes, hyperalgesia, hypogonad- ism, hyponatremia, ileus, intentional overdose, mood altered, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, suicidal attempt, suicidal ideation, syndrome of inappropriate antidiuretic hor- mone secretion, and urticaria.

Anaphylaxis has been reported with ingredi- ents contained in OXYCONTIN. Advise patients how to recognize such a reaction and when to seek medical attention.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swal- lowing the tablet.

## DRUG INTERACTIONS

* 1. **CNS Depressants**

The concomitant use of OXYCONTIN and other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics,

phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma, or death. Monitor patients receiving CNS depressants and OXY- CONTIN for signs of respiratory depression, sedation, and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.6) and Warnings and Precautions (5.4)].*

## Drugs Affecting Cytochrome P450 Isoenzymes

*Inhibitors of CYP3A4 and 2D6*

Because the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that inhibit CYP3A4 activity may cause de- creased clearance of oxycodone 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-administra- tion with OXYCONTIN is necessary, moni-

tor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)].*

*Inducers of CYP3A4*

CYP450 3A4 inducers may induce the me- tabolism 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 depen- dence to oxycodone. If co-administration with

OXYCONTIN is necessary, monitor for signs of opioid withdrawal and consider dose adjust- ments until stable drug effects are achieved.

After stopping the treatment of a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression *[see Clinical Pharmacology (12.3)].*

* 1. **Mixed Agonist/Antagonist and Partial Agonists Opioid Analgesics** Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial ago- nist (buprenorphine) analgesics may reduce the analgesic effect of oxycodone or precipi- tate withdrawal symptoms. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving OXYCONTIN.

## Muscle Relaxants

Oxycodone may enhance the neuromuscu- lar blocking action of true skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and OXYCONTIN for signs of respiratory depression that may be greater than otherwise expected.

## Diuretics

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.

* 1. **Anticholinergics** Anticholinergics or other medications with anticholinergic activity when used concur- rently 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 OXYCONTIN is used concurrently with anticholinergic drugs.

## USE IN SPECIFIC POPULATIONS

* 1. **Pregnancy**

*Clinical Considerations Fetal/neonatal adverse reactions*

Prolonged use of opioid analgesics dur- ing pregnancy for medical or nonmedical

purposes can result in physical dependence in the neonate and neonatal opioid with- drawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and sei- zures, and manage accordingly *[see Warnings and Precautions (5.3)].*

*Teratogenic Effects - Pregnancy Category C* There are no adequate and well-controlled studies in pregnant women. OXYCONTIN

should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

The effect of oxycodone in human reproduc- tion has not been adequately studied. Studies with oral doses of oxycodone hydrochloride in

rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m2 basis, did not reveal evidence

of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no long-term devel- opmental or reproductive effects in the pups *[see Nonclinical Toxicology (13.1)].*

*Non-Teratogenic Effects*

Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used

(6 mg/kg/day, equivalent to approximately 0.4-times an adult human dose of 160 mg/

day, on a mg/m2 basis). However, body weight of these pups recovered.

## Labor and Delivery

Opioids cross the placenta and may pro- duce respiratory depression in neonates. OXYCONTIN is not recommended for use in women immediately prior to labor, when use of shorter-acting analgesics or other analge- sic techniques are more appropriate. Opioid analgesics can prolong labor through actions which temporarily reduce the strength, dura- tion and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

## Nursing Mothers

Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving OXYCONTIN. Do not initiate OXYCONTIN therapy while nursing because of the possibility of sedation or respiratory depression in the infant.

Withdrawal signs can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast- feeding is stopped.

## Pediatric Use

The safety and efficacy of OXYCONTIN have been established in pediatric patients ages 11 to 16 years. Use of OXYCONTIN is supported by evidence from adequate and well-con- trolled trials with OXYCONTIN in adults as well as an open-label study in pediatric patients ages 6 to 16 years. However, there were insufficient numbers of patients less than 11 years of age enrolled in this study to establish the safety of the product in this age group.

The safety of OXYCONTIN in pediatric patients was evaluated in 155 patients previously receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent on the two days immediately preceding dosing with OXYCONTIN. Patients were started on a total

daily dose ranging between 20 mg and 100 mg depending on prior opioid dose.

The most frequent adverse events observed in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Trials (14)].*

## Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma con- centrations of oxycodone were increased ap- proximately 15% *[see Clinical Pharmacology (12.3)].* Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or un- expected adverse reactions were seen in the elderly patients who received oxycodone hy- drochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, re- duce the starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients. Respiratory depression is the chief risk in elderly or debilitated patients, usually the result of large initial doses in patients who are not tolerant to opioids, or when opioids are given in conjunction with other agents that depress respiration. Titrate the dose of OXYCONTIN cautiously in these patients.

## Hepatic Impairment

A study of OXYCONTIN in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)].*

## Renal Impairment

In patients with renal impairment, as evi- denced by decreased creatinine clearance (<60 mL/min), the concentrations of oxyco- done 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 *[see Clinical Pharmacology (12.3)].*

## Gender Differences

In pharmacokinetic studies with OXYCONTIN, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment

for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

## DRUG ABUSE AND DEPENDENCE

* 1. **Controlled Substance** OXYCONTIN contains oxycodone, a Schedule II controlled substance with a high potential for abuse similar to other opioids includ-

ing fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is subject to misuse, addic- tion, and criminal diversion *[see Warnings and Precautions (5.1)].*

The high drug content in extended-release formulations adds to the risk of adverse out- comes from abuse and misuse.

## Abuse

All patients treated with opioids require care- ful monitoring for signs of abuse and addic- tion, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psycho- logical or physiological effects. Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over- the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, dif- ficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activi- ties and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common to addicts and drug abusers. Drug-seeking

tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or refer- ral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple pre- scribers) to obtain additional prescriptions

is common among drug abusers and people suffering from untreated addiction. Preoccu- pation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance.

Physicians should be aware that addiction may not be accompanied by concurrent toler- ance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OXYCONTIN, like other opioids, can be diverted for non-medical use into illicit channels of dis- tribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly advised.

Proper assessment of the patient, proper

prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse of opioid drugs.

*Risks Specific to Abuse of OXYCONTIN* OXYCONTIN is for oral use only. Abuse of OXY- CONTIN poses a risk of overdose and death.

The risk is increased with concurrent use of OXYCONTIN with alcohol and other central nervous system depressants. Taking cut, bro- ken, chewed, crushed, or dissolved OXYCON- TIN enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocardi- tis and valvular heart injury. Parenteral drug abuse is commonly associated with transmis- sion of infectious diseases, such as hepatitis and HIV.

*Abuse Deterrence Studies*

OXYCONTIN is formulated with inactive ingre- dients intended to make the tablet more dif- ficult to manipulate for misuse and abuse. For the purposes of describing the results of stud- ies of the abuse-deterrent characteristics of OXYCONTIN resulting from a change in formu- lation, in this section, the original formulation of OXYCONTIN, which is no longer marketed, will be referred to as “original OxyContin” and the reformulated, currently marketed product will be referred to as “OXYCONTIN”.

*In Vitro Testing*

*In vitro* physical and chemical tablet manipu- lation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formula- tion. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCONTIN relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXY- CONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

*Clinical Studies*

In a randomized, double-blind, placebo- controlled 5-period crossover pharmacody- namic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCONTIN 30 mg tablets, coarsely crushed OXYCONTIN 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OXY- CONTIN, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100

represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale

of 0 to 100 where 50 represents a neutral response, 0 represents the strongest nega- tive response (“definitely would not take drug again”) and 100 represents the strongest positive response (“definitely would take drug again”).

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects’ nostrils occurred in 34% (n = 10) of subjects with finely crushed OXYCONTIN, compared with 7% (n = 2) of subjects with finely crushed original OxyCon- tin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCONTIN was associated with a numerical- ly lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed origi- nal OxyContin or powdered oxycodone HCl as summarized in Table 4.

## Table 4: Summary of Maximum Drug Liking (Emax) Data Following Intranasal Administration

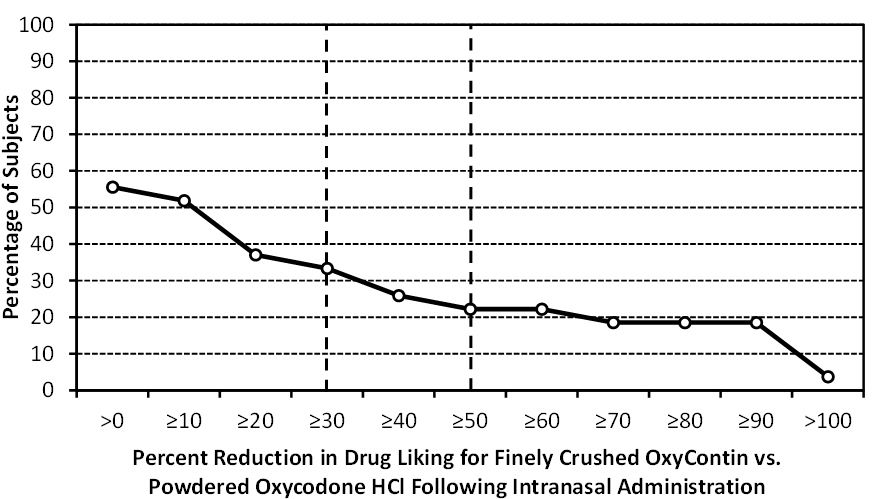
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| VAS Scale (100 mm)\* |  | OXYCONTIN  (finely crushed) | Original OxyContin (finely crushed) | Oxycodone HCl (powdered) |
| Drug Liking | Mean (SE) | 80.4 (3.9) | 94.0 (2.7) | 89.3 (3.1) |
| Median (Range) | 88 (36-100) | 100 (51-100) | 100 (50-100) |
| Take Drug Again | Mean (SE) | 64.0 (7.1) | 89.6 (3.9) | 86.6 (4.4) |
| Median (Range) | 78 (0-100) | 100 (20-100) | 100 (0-100) |

\* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OXYCONTIN compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCONTIN vs. oxycodone HCl powder greater than or equal to the value on the

X-axis. Approximately 44% (n = 12) had no reduction in liking with OXYCONTIN relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OXYCONTIN relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OXYCONTIN compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to oxycodone HCl.

## Figure 1: Percent Reduction Profiles for Emax of Drug Liking VAS for OXY- CONTIN vs. oxycodone HCl, N=27 Following Intranasal Administration



The results of a similar analysis of drug liking for finely crushed OXYCONTIN relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCONTIN relative to powdered oxycodone HCl. Ap- proximately 43% (n = 12) of subjects had no reduction in liking with OXYCONTIN relative

to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and

approximately 29% (n = 8) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to original OxyContin.

*Summary*

The *in vitro* data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the in- tranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current for- mulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OXYCONTIN contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)].*

## Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as

analgesia (in the absence of disease progres- sion or other external factors). Tolerance

may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. With- drawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OXYCONTIN should not be abruptly discon- tinued *[see Dosage and Administration (2.9)].* If OXYCONTIN is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome:

restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis.

Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insom- nia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Popula- tions (8.1)].*

## OVERDOSAGE

***Clinical Presentation***

Acute overdosage with OXYCONTIN can be manifested by respiratory depression,

somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypoten- sion, partial or complete airway obstruction, atypical snoring and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

***Treatment of Overdose***

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors)

in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life sup- port techniques.

The opioid antagonists, naloxone or na- lmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respira- tory or circulatory depression secondary to oxycodone overdose. Such agents should be administered cautiously to persons who are known or suspected to be physically depen- dent on OXYCONTIN. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Because the duration of reversal would be expected to be less than the duration of action of oxycodone in OXYCONTIN, carefully moni- tor the patient until spontaneous respiration

is reliably reestablished. OXYCONTIN will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to opioid antago- nists is suboptimal or not sustained, additional antagonist should be administered as directed in the product’s prescribing information.

In an individual physically dependent on opi- oids, administration of the usual dose of the antagonist will precipitate an acute withdraw- al syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, adminis-

tration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

## DESCRIPTION

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets is an opioid anal- gesic supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:

CH3O

–

O

Cl

+

N CH3

OH H

O

C18 H21 NO4 • HCl MW 351.83

The chemical name is 4, 5*a*-epoxy-14-hy- droxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline pow- der derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7).

The 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablets contain the follow-

ing inactive ingredients: butylated hydroxytol- uene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain hydroxypropyl cellulose.

The 15 mg tablets also contain black iron oxide, yellow iron oxide, and red iron oxide. The 20 mg tablets also contain polysorbate 80

and red iron oxide.

The 30 mg tablets also contain polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

The 40 mg tablets also contain polysorbate 80 and yellow iron oxide.

The 60 mg tablets also contain polysorbate 80, red iron oxide and black iron oxide.

The 80 mg tablets also contain hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/ Indigo Carmine Aluminum Lake.

## CLINICAL PHARMACOLOGY

Oxycodone hydrochloride is a full opioid agonist and is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. Clinically, dosage is titrated to provide adequate analge- sia and may be limited by adverse reactions, including respiratory and CNS depression.

## Mechanism of Action

*Central Nervous System*

The precise mechanism of the analgesic action is unknown. However, specific 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.

## Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OXYCONTIN (10, 20, and 30 mg) in an anal- gesic pain model involving 182 patients with moderate to severe pain. OXYCONTIN doses of

20 mg and 30 mg produced statistically signifi- cant pain reduction compared to placebo.

*Effects on the Central Nervous System* Oxycodone produces respiratory depression by direct action on brain stem respiratory centers.

The respiratory depression involves both a re- duction in the responsiveness of the brain stem respiratory centers to increases in CO2 tension and to electrical stimulation.

Oxycodone depresses the cough reflex by di- rect effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total dark- ness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose *[see Overdosage (10)].*

*Effects on the Gastrointestinal Tract and Other Smooth Muscle*

Oxycodone causes a reduction in motil- ity associated with an increase in smooth muscle tone in the antrum of the stomach

and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves

in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pan- creatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

*Effects on the Cardiovascular System* Oxycodone may produce release of histamine with or without associated peripheral vasodila-

tion. Manifestations of histamine release and/ or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

*Effects on the Endocrine System*

Opioids inhibit the secretion of ACTH, cortisol, testosterone, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secre- tion of insulin and glucagon.

*Effects on the Immune System*

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown.

Overall, the effects of opioids appear to be modestly immunosuppressive.

*Concentration –Efficacy Relationships*

Studies in normal volunteers and patients

reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentra- tion and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective “drug effect”, analgesia and feelings of relaxation.

The minimum effective analgesic concentra- tion will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individual- ized titration of dosage to the desired effect.

The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/ or the development of analgesic tolerance.

*Concentration –Adverse Reaction Relationships* There is a relationship between increasing oxy- codone plasma concentration and increasing

frequency of dose-related opioid adverse reac- tions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related side effects.

The dose of OXYCONTIN must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients *[see Dosage and Administration (2.1)].*

## Pharmacokinetics

The activity of OXYCONTIN is primarily due to the parent drug oxycodone. OXYCONTIN is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dis- solving OXYCONTIN impairs the controlled- release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OXYCONTIN is pH independent. The oral bioavailability of oxyco- done is 60% to 87%. The relative oral bioavail- ability of oxycodone from OXYCONTIN to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OXYCONTIN in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life (t½) of oxycodone following the administration of OXYCONTIN was

4.5 hours compared to 3.2 hours for immedi- ate-release oxycodone.

*Absorption*

About 60% to 87% of an oral dose of oxy- codone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/ or first-pass metabolism.

*Plasma Oxycodone Concentration over Time* Dose proportionality has been established for OXYCONTIN 10 mg, 15 mg, 20 mg, 30 mg, 40

mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (Cmax) and

extent of absorption (AUC) *(see Table 5).* Given the short elimination t½ of oxycodone, steady- state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OXYCONTIN. In a study compar- ing 10 mg of OXYCONTIN every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and Cmax, and similar for Cmin (trough) concentrations.

## TABLE 5

**Mean [% coefficient of variation]**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Regimen** | **Dosage Form** | **AUC Cmax (ng•hr/mL)\* (ng/mL)** | | **Tmax (hr)** |
| Single | 10 mg | 136 [27] | 11.5 [27] | 5.11 [21] |
| Dose† | 15 mg | 196 [28] | 16.8 [29] | 4.59 [19] |
|  | 20 mg | 248 [25] | 22.7 [25] | 4.63 [22] |
|  | 30 mg | 377 [24] | 34.6 [21] | 4.61 [19] |
|  | 40 mg | 497 [27] | 47.4 [30] | 4.40 [22] |
|  | 60 mg | 705 [22] | 64.6 [24] | 4.15 [26] |
|  | 80 mg | 908 [21] | 87.1 [29] | 4.27 [26] |

\* for single-dose AUC = AUC0-inf

† data obtained while subjects received naltrexone, which can enhance absorption

*Food Effects*

Food has no significant effect on the extent of absorption of oxycodone from OXYCONTIN. *Distribution*

Following intravenous administration, the steady-state volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone bind- ing to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.3)].*

*Metabolism*

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymor- phone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A medi- ated *N-*demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated *O-* demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs *[see Drug Interactions (7.3)].*

Noroxycodone exhibits very weak anti-nocicep- tive 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 follow- ing oxycodone administration is thought to be

clinically insignificant. Other metabolites (*a*- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes re- sponsible for keto-reduction and glucuronida- tion pathways in oxycodone metabolism have not been established.

*Excretion*

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts mea- sured 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%. The total plasma clearance was ap- proximately 1.4 L/min in adults.

*Specific Populations Geriatric Use*

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young sub- jects (age 21-45).

*Gender*

Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight-adjusted basis. The reason for this difference is un- known *[see Use in Specific Populations (8.8)].*

*Renal Impairment*

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunc- tion (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respec- tively, and AUC values for oxycodone, noroxy- codone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in seda- tion but not by differences in respiratory rate, pupillary constriction, or several other mea- sures of drug effect. There was an increase in mean elimination t½ for oxycodone of 1 hour.

*Hepatic Impairment*

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respec- tively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymor- phone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination t½ for oxycodone increased by 2.3 hours.

*Pediatric Use*

In the pediatric age group of 11 years of age and older, systemic exposure of oxycodone is expected to be similar to adults at any given dose of OXYCONTIN.

*Drug-Drug Interactions CYP3A4 Inhibitors*

CYP3A4 is the major isoenzyme involved in noroxycodone formation. Co-administration

of OXYCONTIN (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and Cmax by 170% and 100%, respectively *[see Drug Interactions (7.2)].*

*CYP3A4 Inducers*

A published study showed that the co-adminis- tration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and Cmax values by 86% and 63%, respectively *[see Drug Interactions (7.2)].*

*CYP2D6 Inhibitors*

Oxycodone is metabolized in part to oxymor- phone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and an- tidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical signifi- cance with OXYCONTIN *[see Drug Interactions (7.2)].*

## NONCLINICAL TOXICOLOGY

* 1. **Carcinogenesis, Mutagenesis, Impairment of Fertility**

*Carcinogenesis*

No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.  *Mutagenesis*

Oxycodone was genotoxic in the mouse lymphoma assay at concentrations of 50 mcg/ mL or greater with metabolic activation and

at 400 mcg/mL or greater without metabolic activation. Clastogenicity was observed with oxycodone in the presence of metabolic activa- tion in one chromosomal aberration assay in human lymphocytes at concentrations greater than or equal to 1250 mcg/mL at 24 but not 48 hours of exposure. In a second chromosomal aberration assay with human lymphocytes, no structural clastogenicity was observed either with or without metabolic activation; how- ever, in the absence of metabolic activation, oxycodone increased numerical chromosomal aberrations (polyploidy). Oxycodone was not genotoxic in the following assays: Ames *S. typhimurium* and *E. coli* test with and without metabolic activation at concentrations up to 5000 µg/plate, chromosomal aberration test in human lymphocytes (in the absence of meta- bolic activation) at concentrations up to 1500

µg/mL, and with activation after 48 hours of exposure at concentrations up to 5000 µg/mL, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels up to 48 µg/ mL).

*Impairment of Fertility*

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg/day). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to gestation day 6. Oxyco- done hydrochloride did not affect reproductive function in male or female rats at any dose tested (≤8 mg/kg/day).

## CLINICAL STUDIES

**Adult clinical study**

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inad- equate pain control with their current therapy. In this study, OXYCONTIN 20 mg, but not 10 mg, was statistically significant in pain reduc- tion compared with placebo.

**Pediatric clinical study**

OXYCONTIN has been evaluated in an open-la- bel clinical trial of 155 opioid-tolerant pediatric patients with moderate to severe chronic pain. The mean duration of therapy was 20.7 days (range 1 to 43 days). The starting total daily doses ranged from 20 mg 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). In an extension study, 23 of the 155 patients were treated beyond four weeks, including 13 for 28 weeks. Too few patients less than 11 years were enrolled in the clinical trial to pro- vide meaningful safety data in this age group.

## HOW SUPPLIED/STORAGE AND HANDLING

OXYCONTIN (oxycodone hydrochloride) extend- ed-release tablets 10 mg are film-coated, round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other and are sup- plied as child-resistant closure, opaque plastic bottles of 100 **(NDC 59011-410-10)** and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton **(NDC 59011-410-20).**

OXYCONTIN (oxycodone hydrochloride) extend- ed-release tablets 15 mg are film-coated, round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other and are sup- plied as child-resistant closure, opaque plastic bottles of 100 **(NDC 59011-415-10)** and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton **(NDC 59011-415-20).**

OXYCONTIN (oxycodone hydrochloride) extend- ed-release tablets 20 mg are film-coated, round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other and are sup- plied as child-resistant closure, opaque plastic bottles of 100 **(NDC 59011-420-10)** and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton **(NDC 59011-420-20).**

OXYCONTIN (oxycodone hydrochloride) extend- ed-release tablets 30 mg are film-coated, round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other and are sup- plied as child-resistant closure, opaque plastic bottles of 100 **(NDC 59011-430-10)** and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton **(NDC 59011-430-20).**

OXYCONTIN (oxycodone hydrochloride) extend- ed-release tablets 40 mg are film-coated, round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other and are sup- plied as child-resistant closure, opaque plastic

bottles of 100 **(NDC 59011-440-10)** and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton **(NDC 59011-440-20).**

OXYCONTIN (oxycodone hydrochloride) extend- ed-release tablets 60 mg are film-coated, round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other and are sup- plied as child-resistant closure, opaque plastic bottles of 100 **(NDC 59011-460-10)** and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton **(NDC 59011-460-20).**

OXYCONTIN (oxycodone hydrochloride) extend- ed-release tablets 80 mg are film-coated, round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other and are sup- plied as child-resistant closure, opaque plastic bottles of 100 **(NDC 59011-480-10)** and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton **(NDC 59011-480-20).**

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

## CAUTION

**DEA FORM REQUIRED**

1. **PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

*Addiction, Abuse and Misuse*

Inform patients that the use of OXYCONTIN, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings*

*and Precautions (5.1)].* Instruct patients not to share OXYCONTIN with others and to take steps to protect OXYCONTIN from theft or misuse.

*Life-Threatening Respiratory Depression* Inform patients of the risk of life-threatening respiratory depression including information that the risk is greatest when starting OXY- CONTIN or when the dose is increased and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)].* Advise patients how to recognize respiratory depres- sion and to seek medical attention if breathing difficulties develop.

To guard against excessive exposure to OXY- CONTIN by young children, advise caregivers to strictly adhere to recommended OXYCON- TIN dosing.

*Accidental Ingestion*

Inform patients that accidental ingestion, especially in children, may result in respira- tory depression or death *[see Warnings and Precautions (5.2)].* Instruct patients to take steps to store OXYCONTIN securely and to dispose of unused OXYCONTIN by flushing the tablets down the toilet.

*Neonatal Opioid Withdrawal Syndrome* Inform female patients of reproductive potential that prolonged use of OXYCONTIN

during pregnancy can result in neonatal opioid

withdrawal syndrome, which may be life- threatening if not recognized and treated *[see Warnings and Precautions (5.3)].*

*Interactions with Alcohol and other CNS Depressants*

Inform patients that potentially serious addi- tive effects may occur if OXYCONTIN is used with other CNS depressants, and not to use such drugs unless supervised by a health care provider.

*Important Administration Instructions* Instruct patients how to properly take OXY- CONTIN, including the following:

* OXYCONTIN is designed to work prop- erly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN tablets can result in a fatal overdose.
* OXYCONTIN tablets should be taken one tablet at a time.
* Do not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth.
* Take each tablet with enough water to en- sure complete swallowing immediately after placing in the mouth.

*Hypotension*

Inform patients that OXYCONTIN may cause orthostatic hypotension and syncope. In- struct patients how to recognize symptoms of low blood pressure and how to reduce the

risk of serious consequences should hypoten- sion occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

*Driving or Operating Heavy Machinery* Inform patients that OXYCONTIN may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to

perform such tasks until they know how they will react to the medication.

*Constipation*

Advise patients of the potential for severe constipation, including management instruc- tions and when to seek medical attention.

*Anaphylaxis*

Inform patients that anaphylaxis has been re- ported with ingredients contained in OXYCON- TIN. Advise patients how to recognize such a reaction and when to seek medical attention.

*Pregnancy*

Advise female patients that OXYCONTIN can cause fetal harm and to inform the prescriber if they are pregnant or plan to become preg- nant.

*Disposal of Unused OXYCONTIN*

Advise patients to flush the unused tablets down the toilet when OXYCONTIN is no longer needed.

Healthcare professionals can telephone Purdue Pharma’s Medical Services Department (1-888-726-7535) for information on this product.

**Purdue Pharma L.P. Stamford, CT 06901-3431**

©2015, Purdue Pharma L.P.

U.S. Patent Numbers 6,488,963; 7,129,248;

7,674,799; 7,674,800; 7,683,072; 8,114,383;

8,309,060; 8,337,888; 8,808,741; 8,821,929;

8,894,987; 8,894,988; 9,060,976; and

9,073,933.

|  |
| --- |
| **Medication Guide**  **OXYCONTIN® (ox-e-KON-tin)**  **(oxycodone hydrochloride) extended-release tablets, CII** |
| **OXYCONTIN is:**   * A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them. * A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death. * Not for use to treat pain that is not around-the-clock. * Not for use in children less than 11 years of age and who are not already using opioid pain medicines regularly to manage pain severe enough to require daily around-the-clock long-term treatment of pain with an opioid. |
| **Important information about OXYCONTIN:**   * **Get emergency help right away if you take too much OXYCONTIN (overdose).** When you first start taking OXYCONTIN, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. * Never give anyone else your OXYCONTIN. They could die from taking it. Store OXYCONTIN away from children and in a safe place to prevent stealing or abuse. Selling or giving away OXYCONTIN is against the law. |
| **Do not take OXYCONTIN if you have:**   * severe asthma, trouble breathing, or other lung problems. * a bowel blockage or have narrowing of the stomach or intestines. |
| **Before taking OXYCONTIN, tell your healthcare provider if you have a history of:**   * head injury, seizures * liver, kidney, thyroid problems * problems urinating * pancreas or gallbladder problems * abuse of street or prescription drugs, alcohol addiction, or mental health problems.   **Tell your healthcare provider if you are:**   * **pregnant or planning to become pregnant.** Prolonged use of OXYCONTIN during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. * **breastfeeding.** OXYCONTIN passes into breast milk and may harm your baby. * taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OXYCONTIN with certain other medicines can cause serious side effects that could lead to death. |
| **When taking OXYCONTIN:**   * Do not change your dose. Take OXYCONTIN exactly as prescribed by your healthcare provider. * Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time. * Swallow OXYCONTIN whole. Do not cut, break, chew, crush, dissolve, snort, or inject OXYCONTIN because this may cause you to overdose and die. * OXYCONTIN should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet. * **Call your healthcare provider if the dose you are taking does not control your pain.** * **Do not stop taking OXYCONTIN without talking to your healthcare provider.** * After you stop taking OXYCONTIN, flush any unused tablets down the toilet. |
| **While taking OXYCONTIN DO NOT:**   * Drive or operate heavy machinery until you know how OXYCONTIN affects you. OXYCONTIN can make you sleepy, dizzy, or lightheaded. * Drink alcohol, or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with OXYCONTIN may cause you to overdose and die. |
| **The possible side effects of OXYCONTIN are:**   * constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.   **Get emergency medical help if you have:**   * trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.   These are not all the possible side effects of OXYCONTIN. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**  Manufactured by: Purdue Pharma L.P., Stamford, CT 06901-3431, [**www.purduepharma.com**](http://www.purduepharma.com/) **or call 1-888-726-7535** |

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 08/2015





302940-0G 0PO519