

Exhibit 2

To Citizen Petition
Docket No. 2004P-0006
June 4, 2007

OxyContin[®] (oxycodone HCl controlled-release) Tablets
RISK MANAGEMENT PROGRAM

Revised 18 May 2007

1. INTRODUCTION

This risk management program has been designed to address four key potential risk situations, involving four populations.

- Patients (proper patient selection, dosing and adherence)
- Children (avoiding exposure)
- Abusers (reduction of abuse, along the spectrum from experimenter to addict)
- Criminals (reduction of diversion)

Purdue Pharma L.P. has designed and developed a state-of-the-art, comprehensive program with the overarching goal of making every reasonable effort to reduce the risk of potential untoward events with OxyContin[®] Tablets. The objectives to achieve the goal of this risk management program are geared toward prevention of untoward events through product labeling, training of sales representatives, proper promotion of OxyContin[®] Tablets, education of prescribers, information for patients and caregivers, and appropriate interventions when surveillance has detected occurrence of significant abuse or identification of significant risk for abuse. Each ongoing component of this program will be assessed on a regular basis and modified, if necessary, based on knowledge gained.

The purpose of this risk management program is to help ensure the safe use of OxyContin[®] Tablets. This risk management program will not be used in a promotional context.

2. KEY SAFETY MESSAGES

There are several key messages repeated throughout this risk management program. These messages include

- Proper patient selection messages

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen, to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

- Safety and effectiveness of OxyContin[®] have not been established in patients below the age of 18.
- OxyContin[®] Tablets must not be crushed or divided for oral administration.
- OxyContin[®] Tablets are a controlled-release formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous,

around-the-clock analgesic is needed for an extended period of time.

- OxyContin[®] is NOT intended for use as a prn analgesic.
- OxyContin[®] is not indicated for pain in the immediate postoperative period (for the first 12 to 24 hours following surgery), or if the pain is mild or is not expected to persist for an extended period of time.
- OxyContin[®] 80mg Tablets are for use in opioid-tolerant patients only. These are patients who have been receiving opioid therapy at the equivalent of 160 mg of oxycodone or greater for at least one week. This tablet strength may cause respiratory depression when administered to patients not previously exposed to opioids.
- Taking broken, chewed, or crushed OxyContin[®] Tablets leads to the rapid release and absorption of a potentially fatal dose of oxycodone.
- Minimization of diversion and abuse
 - OxyContin[®] is to be used only by patients for whom it is dispensed.
 - OxyContin[®] is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Schedule II substances are those considered to have a high abuse potential. Criminal penalties apply if a controlled substance is unlawfully distributed.
 - The appropriate use of OxyContin[®] Tablets includes proper disposal of unused medication.
 - Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.
- Child safety
 - OxyContin[®] Tablets must be kept out of the reach of children.
 - OxyContin[®] Tablets must be properly stored and handled.
 - The appropriate use of OxyContin[®] Tablets includes proper disposal of unused medication.
 - Healthcare professionals should counsel patients on child safety messages.
 - Safety and effectiveness of OxyContin[®] have not been established in patients below the age of 18.

3. PRODUCT DEFINITION

OxyContin[®] (oxycodone HCl controlled-release) Tablets are an opioid analgesic supplied in 10-, 20-, 40- and 80-mg tablet strengths for oral administration. Each tablet contains the nominal amount of oxycodone, indicated by the strength, as the hydrochloride salt. Dose proportionality has been established for the 10-, 20-, 40-, and 80-mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC). OxyContin[®] 10 mg every 12 hours was found to be equivalent to 5 mg of immediate-release oxycodone every 6 hours in AUC and C_{max} , and similar for C_{min} (trough) concentrations.

3.1. OxyContin[®] Tablets

Control of the release of oxycodone from OxyContin[®] is achieved by formulating the active ingredient in a dual-polymer matrix. The tablet must be taken intact for the release of oxycodone to be controlled as intended.

3.2. Safety Features of Packaging

OxyContin[®] Tablets are packaged by the manufacturer in child-resistant bottles and blister packs. The 80mg strength displays a red triangle with the message "for use in opioid tolerant patients." OxyContin[®] Tablets may be repackaged according to local pharmacy practice for dispensing to patients.

3.3. Disposal of Unused Product

Unused medication should be disposed of promptly by flushing the intact tablets down the toilet. The Patient Package Insert includes a message on disposal of unused tablets. This Patient Package Insert is available to patients and caregivers through their healthcare professionals. These instructions are consistent with recently released joint recommendations from ONDCP, EPA and FDA.

3.4 Supply Chain Integrity

Our Corporate Security department has instituted procedures within the manufacturing facilities that serve to reduce the likelihood of opportunistic and calculated diversion of controlled substances that go beyond the minimum legal requirements, such as controlled substance accountability and caged storage.

3.4.1 Personnel

To reduce opportunistic diversion, Purdue conducts background checks on all people who have access to controlled substances in our plants.

3.4.2 Site Security Measures

Purdue has instituted a number of security measures that exceed minimum requirements of law and regulation, including, but not limited to:

- Color-coded uniforms that match areas to which workers in a given color have access. This allows quick recognition by security cameras of persons in areas for which they do not have authorization.
- Pocketless uniforms are mandated, reducing opportunistic diversion
- Biometric access for sensitive areas
- In the newest plant (Wilson, NC) the design is such that access for 80+% of routine maintenance of machinery does not allow maintenance workers access to controlled substances.
- Video surveillance of all packaging and shipping operations.

3.4.3 Transit Security Measures

Purdue has instituted policies and procedures to protect the product as it is shipped to wholesalers, including, but not limited to:

- RFID tags in certain bottle labels
- The use of carefully selected couriers for transport of product to the first node in the supply chain – including criminal background checks on drivers
- GPS tracking of certain pallets
- GPS tracking of certain trucks, coupled with designated routes and timed itineraries
- Intermittent use of unmarked, unannounced surveillance vehicle to track courier tractor-trailers

3.4.4 Anti-Counterfeiting Measures

Purdue has instituted a vigorous program to thwart those who would counterfeit the product and, thereby, threaten the integrity of the supply and the safety of patients, including, but not limited to:

- Color-shifting ink on product bottle labels
- Covert anti-counterfeiting feature on product bottle labels
- Assistance to law enforcement agencies investigating suspected counterfeiting, including:
 - Technical consultation regarding investigation of counterfeiting
 - Coordination between various agencies and jurisdictions
 - Chemical and physical analysis of counterfeit product, including “chemical fingerprinting” and near-IR spectroscopy of intact product

4. LABELING

4.1. Scheduling

The US Drug Enforcement Administration places very specific controls on the storage, distribution, accountability, prescribing, and use of scheduled products (see 21CFR1301, et seq.). OxyContin[®] is a product subject to Schedule II (CII) controls under the Controlled Substances Act, consistent with other drug products containing strong opioids such as fentanyl, morphine, oxymorphone and hydromorphone.

CII is the most restrictive classification available for approved products, and raises the overall level of vigilance and surveillance by all parties involved with the product. These restrictions include:

- Strongest tracking and controls throughout the distribution system;
- Clear “CII” notation in the labeling and on product packaging;
- One hundred percent drug accountability by individual count to the pharmacy level;
- Most stringent physical storage requirements until dispensing to the patient;
- No refills allowed;
- Healthcare professionals cannot call in prescriptions (except in emergency situations);
- Registered pharmacist to ensure a legitimate medical purpose before dispensing.

The status of OxyContin as a CII product is an important risk management element guarding against the potential of diversion and abuse.

4.2. Full Prescribing Information (Package Insert)

The package insert for OxyContin[®] Tablets clearly and explicitly communicates the key safety messages of this risk management program on proper patient selection, child safety, prevention of abuse, and prevention of diversion. The package insert highlights the risks associated with OxyContin[®] Tablets and the requirements that must be met by healthcare professionals and patients to use OxyContin[®] Tablets in a safe manner. The key elements in the package insert include:

- *Indication.* OxyContin[®] Tablets are a controlled-release formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
- Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as nonsteroidal anti-inflammatory drugs and acetaminophen, to opioids in a plan of pain management

such as outlined by the World Health Organization, Federation of State Medical Boards Model Guidelines, or American Pain Society.

- Boxed warning
- Instructions which minimize the potential for accidental overdose, abuse, diversion, or inadvertent exposure, including exposure to children;
- Instructions for safe handling and storage;
- Instructions for disposal of unused medication;
- CII designation;
- *Drug Abuse and Addiction Section*;
- *Misuse, Abuse, and Diversion of Opioids Section*;

The current package insert is attached as Appendix 1.

4.3. Patient Package Insert

The Patient Package Insert portion of the package insert emphasizes the key safety messages related to the use of the product including the messages of this risk management program. The current Patient Package Insert is also included in Appendix 1.

5. HEALTHCARE PROFESSIONAL EDUCATION

5.1. Accredited Continuing Education Programs

Purdue Pharma L.P. provides educational grants in support of continuing education (CE) programs to teach healthcare professionals how to properly assess and treat patients with persistent pain. These educational programs are conducted according to CE standards (ACCME for physicians, ACPE for pharmacists, ANCC for nurses, etc) and, therefore, are not product-specific. Because the management of persistent moderate to severe pain often requires an interdisciplinary approach, these programs are typically designed to inform a broad healthcare audience. In these programs, the presenters almost always recommend individualized treatment in every case following a pain management plan consistent with published guidelines. CE programs on pain management that discuss the use of opioid analgesics often address the issues surrounding the potential misuse, abuse, addiction, and diversion of these products.

Purdue Pharma L.P. is committed to minimizing any illicit use of our products. Examples of the types of programs that we support are discussed in the following sections.

5.1.1. Symposia at National / Regional Organization / Society Meetings

Each year we support many programs on a national and regional basis, and include lectures on ways for healthcare professionals to minimize abuse, misuse and diversion of opioids. Presentations by law enforcement representatives are included in selected programs.

5.1.2. Seminars

A number of seminar programs are conducted across the country for healthcare professionals each year. These programs may consist of half-day, full-day, or multiple-day programs at local hospitals, society chapter meetings, and statewide organizations. These programs typically include lectures on ways for healthcare professionals to minimize abuse, misuse, and diversion of opioids. Selected meetings include presentations by current or former law enforcement officials.

5.1.3. Monographs

The American Pharmaceutical Association (APhA) developed a continuing education monograph, *Pharmacists' Responsibilities in Managing Opioids: a Resource.* This monograph educates pharmacists about the regulatory aspects of pain management, and is available on the APhA Web site and is distributed to community pharmacists nationwide. APhA published this monograph in February, 2002.

In addition, Purdue provided an educational grant to Albert Einstein College of Medicine in support of a monograph entitled "Substance Abuse Among Health Care Professionals: Recognition and Management". This monograph familiarizes healthcare professionals with substance abuse, potential risk factors, signs and symptoms of addiction, steps for intervention and available sources of professional help. This monograph was released December 2001.

5.1.4. *Clinical Journal of Pain* Supplement (18(4) July/August 2002)

A grant was provided to the *Clinical Journal of Pain* to develop a peer-reviewed, CE-accredited supplement, *Addiction and Pain: Assessment and Treatment Issues*. This supplement was distributed to the 2572 pain medicine specialists, anesthesiologists, and surgeons who comprise the journal's circulation. This enduring material contains manuscripts submitted by invited authors on the following topics:

- Opioid Mechanisms in Analgesia and Addiction—Pharmacotherapy Considerations
- Assessment of Addiction
- Assessment and Treatment of Comorbid Psychiatric Disorders in an Opioid-dependent Population
- Abuse Liability in Opioid Therapy for Pain Treatment in Patients With an Addiction History
- Opioid Therapy Contracts
- Psychological Assessment of Chronic Pain Patients on Opioid Therapy
- Addiction Issues in Cancer Pain Patients
- Treating HIV Patients
- Cognitive Effects of Chronic Opioid Therapy
- Urinary Toxicology Research in Patients With Chronic Noncancer Pain Maintained on Opioids.
- Legal and Administrative Issues in the Use of Opioids for Pain Treatment in Opioid-maintained Addicts
- Ethical Considerations in Treating Addicted Pain Patients

5.2. Non-accredited Education Programs and Activities

Purdue Pharma L.P. also conducts educational programs that are not accredited for continuing education purposes. Our non-accredited educational programs are generally unbranded; when our products are mentioned, we require that the information presented be consistent with labeling. We include information on abuse, misuse, addiction, and diversion in many of these programs.

We provide law enforcement agencies or associations with educational seminars on the use, misuse, abuse, and diversion of OxyContin[®] Tablets.

5.2.1. Targeted Anti-Diversion Programs

Where diversion becomes apparent (e.g., through the media, contacts with law enforcement, treatment professionals, etc), Purdue Pharma L.P. has developed specific anti-diversion educational programs in cooperation with law enforcement officials, state medical/pharmacy/nursing boards, and state departments of justice as well as state attorneys general. Many programs aimed at preventing diversion of prescription medications are conducted each year.

Materials were developed summarizing Purdue supported anti-diversion and law enforcement seminars. By conducting these programs locally, an effort is made to involve primary care practitioners.

5.2.2. Law Enforcement Liaison & Educational Program

Recognizing the pivotal role that law enforcement plays in managing risk associated with manufacturing and legally distributing opioid analgesics, PPLP has instituted two programs to address different aspects of relationships with the law enforcement community.

The first, the Law Enforcement Liaison & Education (LELE) program, a unit of the Corporate Security Department, was instituted in late 2001. This program employs individuals who formerly worked as sworn officers and who have experience in dealing with the diversion of pharmaceutical drugs. The role of these personnel is wide-reaching and includes:

- Educational programs for two target audiences:
 - Healthcare professionals – This is summarized in the anti-diversion programs, where frequently one of the speakers is an individual from the LELE group.
 - Law Enforcement Professionals – When invited to do so, the LELE group, occasionally with a physician from the Risk Management & Health Policy department, will provide educational programs for command or line officers on the appropriate use of medications for pain, guidelines from third parties (scientific associations, medical boards, etc), investigation of diversion, prevention of diversion, understanding addiction, etc. Several lectures by this group are given each year.
- Distribution of the National Association of Drug Diversion Investigators, Inc. (NADDI) Abused Pharmaceutical Brochures. Funded by an unrestricted grant from PPLP, these brochures feature life-sized color photographs of over 30 medicines chosen by NADDI as being diverted to a significant degree. The LELE group has distributed many thousands of these brochures in addition those distributed by NADDI directly.

5.2.3. Medical Liaison Educational Programs

These programs consist of 1-2 hour presentations given at local hospitals, state professional society meetings and statewide organizations are provided by doctoral-level pharmacists or advanced practice nurses employed as Medical Liaisons by Purdue Pharma L.P. The programs are typically focused on issues relating to pain management, including: proper assessment of the person with pain, appropriate pain management therapy options, prevention of abuse and diversion, and the relevant regulatory and legal issues. The Medical Liaisons are also available for one-to-one education sessions with healthcare professionals.

5.2.4. Internet Resources

A CD-ROM was developed entitled "Reducing Misuse, Abuse and Diversion of Opioids through Internet Education". This CD provides live links to Internet sites to aid healthcare professionals in finding pertinent information on the Internet.

Numerous other links are available via the Medical Education Resources Catalog, which is updated at least semi-annually and is available for download at:

5.3. Initiatives Focused on Reducing Abuse and Diversion

Purdue Pharma L.P. has undertaken several risk-reduction initiatives, including printing and distributing anti-diversion brochures and other educational material to the medical community. These materials (one example is described below) form the educational core around which we build our risk reduction efforts. Their focus, along with sound labeling, promotion, and educational programs, is designed to minimize the risk of misuse, abuse, and diversion of our products by emphasizing appropriate use. These materials will be revised as appropriate for continued use in the OxyContin[®] Tablets Risk Management Program.

The “How to Stop Drug Diversion and Protect your Patient” brochure is available to facilitate communication between the prescriber and the patient who requires an opioid analgesic for pain management. Topics include:

- How to Communicate Clearly
- Collecting Information You Need From Patients
- Give Patients the Information They Need
- Emphasize the Most Important Messages
- Provide Clear Messages for Patients Taking Opioid Analgesics for Chronic Pain
- Offer Information to Relieve Your Patient’s Concerns

In addition, a removable information pamphlet located on the back of the brochure may be given to the patient under the healthcare practitioner’s guidance that addresses “How to Take the Medicine Your Doctor has Prescribed”. It covers 22 topics such as:

- Take medication in the prescribed amounts and on the correct schedule.
- Storing medication in a locked place, if possible
- Destroy any unused medication that is no longer needed
- Contact your doctor immediately to report any adverse events, etc.

Based on feedback from health care professionals, a photographic brochure was created, entitled “Providing Relief, Preventing Abuse”, which demonstrates some of the physical stigmata of drug abuse to aid in the assessment of persons presenting with requests for pain control.

6. PATIENT AND CAREGIVER EDUCATION

Patient and caregiver information in the form of a Patient Package Insert has been developed and was approved by FDA in correspondence dated January 15, 2002. This insert conveys information required to assure that patients use OxyContin[®] Tablets properly and safely.

7. PROMOTIONAL PROGRAM

All promotional materials emphasize the key safety messages including information on the potential for misuse, abuse, and diversion of the product in addition to proper patient selection, careful and continuing assessment of pain, and the appropriate use of OxyContin® for the treatment of pain in accordance with current labeling.

Purdue Pharma L.P. promotes the use of OxyContin® Tablets in accordance with the package insert and consistent with FDA promotional regulations.

All printed sales materials used by personnel in a sales or promotional context are reviewed internally by our Medical Affairs, Regulatory Affairs, and Law departments prior to use.

Failure to promote products according to approved labeling, promotional materials, and applicable agency standards will result in appropriate disciplinary action by the company.

Purdue is firmly committed to maintaining the highest standards of marketing practices in the industry while continuing to advance the proper treatment of pain in America. If practitioners believe that Purdue's marketing and sales practices fail to meet this standard, they are urged to report such activity using the toll-free number provided so it can be dealt with immediately. Responses to this program will be used to monitor practitioners' perceptions of detailing messages.

Purdue Pharma L.P. does not conduct brand-specific, direct-to-consumer advertising for our CII opioid analgesics.

7.1. Sales Force Training

Purdue Pharma L.P. trains sales representatives on the specifics of labeling, appropriate use of opioid analgesics, legal guidelines associated with promotion, and their responsibility and role in reporting adverse events. In addition, Sales Representatives are provided training on opioid abuse, misuse, addiction and diversion. Our rigorous standards for the promotion of our products by our sales representatives meet or exceed FDA guidelines for the promotion of prescription drugs. All product claims by our representatives must be consistent with product labeling, including statements concerning the potential of our products for misuse, abuse, overdose, and addiction.

8. SURVEILLANCE GOALS AND ACTIVITIES

The goals of the surveillance and monitoring program are to

- Determine the effectiveness of the risk management program by monitoring the incidence and outcome of misuse, abuse, addiction, diversion, and inadvertent childhood exposure, particularly focusing on mortality from overdose and incidence of new cases of addiction.

- Trigger intervention when problems are discovered;
- Make modifications to the risk management program to improve its effectiveness.

The following sections summarize the various means by which OxyContin[®] use and safety data will be collected and analyzed.

8.1. Product Inquiries

A single telephone number is currently available and is staffed 24 hours a day by healthcare professionals trained in the issues of OxyContin[®] Tablets. This staff (1) provides medical information to healthcare professionals, (2) receives adverse event information, and (3) receives product complaints. Questions and responses are documented and analyzed in an ongoing fashion. Adverse events are brought to the attention of the Drug Safety and Pharmacovigilance Department for processing.

For individual medical emergencies, patients are advised (in the Patient Package Insert) to contact 911 or their local emergency number; healthcare professionals should contact their local Poison Control Center, if appropriate to the emergency situation.

8.2. Media Surveillance

Purdue Pharma L.P. will continue to monitor broadcast and print media as well as professional publications for information on our company and OxyContin[®] Tablets. As part of standard ongoing pharmacovigilance, Purdue will also continue to survey MEDLINE and EMBASE regularly for reports of use, misuse, abuse, addiction, overdose, and diversion involving OxyContin[®] Tablets in the medical literature.

8.3. Exposure Data

Purdue Pharma L.P. reviews data from proprietary sources for OxyContin[®] Tablets on an ongoing basis. Examples of the types of sources that have been reviewed in the past include:

- National Prescription Audit (NPA), a service of IMS HEALTH, which measures the volume of prescriptions dispensed from retail pharmacies to consumers;
- National Disease and Therapeutic Index (NDTI), also a service of IMS HEALTH that is a continuing survey of the patterns and treatment of disease encountered in office-based practice in the continental United States;

8.4. Basic Surveillance for Abuse and Addiction

Basic surveillance for abuse and addiction involving OxyContin[®] Tablets will continue to be conducted using publicly available national surveys. Examples of the data sources that may be used include:

- Drug Abuse Warning Network (DAWN), an estimate of drug-related morbidity from a national probability sample of short-stay, non-federal hospitals with 24 h/d Emergency Departments, sponsored by the Office of Applied Studies of the Substance Abuse and Mental Health Services Administration (SAMHSA)
- Spontaneous adverse events from post-marketing surveillance. This system includes spontaneous reports received directly by Purdue (corporate office) as well as those received from sales force contacts with healthcare professionals.
- The National Survey on Drug Use and Health (NSDUH) is an annual survey of over 60,000 individuals that studies patterns of non-medical use of both licit and illicit drugs in the population aged 12 years and older, sponsored by the Office of Applied Studies of the Substance Abuse and Mental Health Services Administration (SAMHSA)

8.5. RADARS[®] System¹

As of 1 January 2006, the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS[®]) System, initially established by Purdue Pharma L.P., was acquired by the Rocky Mountain Poison and Drug Center, a unit of the not-for-profit Denver Health and Hospital Authority (Denver Health). The System is now owned and operated by Denver Health. This move has allowed the System to attract other pharmaceutical companies as subscribers.

The System is intended to provide timely, sensitive and geographically-specific estimates of the rates of abuse, addiction, and diversion of the RADARS[®] System Monitored Opioids Panel that include the opioid analgesics in Purdue's currently marketed opioid line, as well as other opioid-containing drug products marketed by other sponsors.

8.5.1. Goals of the RADARS[®] System

- Establish a proactive surveillance system for abuse, addiction, and diversion of the RADARS[®] System drugs
 - RADARS[®] System Monitored Opioids Panel includes branded and generic formulations containing the following drug substances: 1) buprenorphine, 2) fentanyl, 3) hydrocodone, 4) hydromorphone, 5) methadone, 6) morphine, 7) oxycodone and 8) tramadol
- Calculate and monitor rates of abuse and diversion on a national and local level utilizing several different denominators (see also 8.5.4)
 - Population within a 3-digit ZIP Code
 - URDDs – Unique Recipients of Dispensed Drugs – data on unique persons who received prescriptions for the Monitored Opioids Panel during a given calendar quarter
 - Other metrics may be explored in the future

- Compute and monitor rates of diversion of RADARS[®] System drugs based on population
- Characterize the trends and cases on a local and national basis as quickly as possible
- Recommend interventions to minimize abuse, addiction and diversion
- Assess effectiveness of interventions

To carry out the goals of the RADARS[®] System, a Scientific Advisory Board (SAB) was established to oversee the development of the studies to collect and analyze the data, recommend interventions when appropriate, and follow up to determine the effectiveness of the interventions. The RADARS[®] System SAB was originally convened in June 2001. Initially, the SAB met approximately monthly and continues to meet on a periodic basis, under the auspices of Denver Health.

Invitations to attend certain quarterly meetings of the SAB have been extended to FDA, ONDCP, NDIC, NIDA, CSAT, CSAP and DEA to join the RADARS[®] SAB. Representatives from NIDA, CSAT, FDA, DEA and CSAP have attended several SAB meetings.

The processes of the RADARS[®] System are dynamic and evolving as needed. There are no models developed to describe the exact procedures to be followed in a post-marketing surveillance program of this type. The only programs to date on which there is published information were designed to monitor the abuse of 1) a non-scheduled drug, tramadol and 2) a schedule IV drug, sibutramine.² It is not clear whether these models are appropriate for monitoring of abuse related to schedule II and III drugs. In addition, both the tramadol and sibutramine post-marketing analyses were studying a single drug not available in multiple generic formulations, whereas the RADARS[®] System is looking at multiple drugs with large numbers of generic formulations as well as branded compounds. This adds significant confounding variables to the process that will require continuous monitoring to assure its effectiveness. The RADARS[®] System SAB continually monitors the appropriateness and effectiveness of the program and each of the studies so that they can be modified to maintain their effectiveness in data collection and development of appropriate interventions. Therefore, the process will be in evolution with changes based on what is learned from the ongoing studies.

8.5.2. RADARS[®] System Signal Detection Studies

Four signal detection studies have been funded to proactively collect data on abuse, addiction and diversion of the RADARS[®] System Monitored Opioids Panel. Abuse and addiction determinations are made using DSM-IV-TR criteria whenever possible.³

Data are collected and reported to the SAB and the Industry Advisory Board (IAB – comprising representatives of each subscriber to the System) on a quarterly basis. The studies are designed to provide information from as wide a geographic area as possible and include data reporters from urban, suburban and rural areas.

The SAB initially determined that a positive signal for a problem will be based on the combined information from the four signal detection studies: five or more cases of abuse, diversion or addiction per 100,000 population in the 3-digit ZIP Code area where the cases have been uncovered are currently used for the Key Informant, Drug Diversion and DENS studies. A level of two or more cases per 100,000 population in a 3-digit ZIP Code is currently used for the Poison Control Center study. These extremely sensitive signal detection levels may be modified in the future based on assessment of these studies.

8.5.2.1. Signal Detection Studies⁴

1. The Key Informant Network Signal Detection System – Theodore Cicero, Ph.D. (Washington Univ., St. Louis). Approximately 250 key informants were recruited from broad geographic areas including urban, suburban and rural locations and practitioners of various specialties. These include NIDA grantees involved in clinical and ethnographic studies, pain specialists, addiction treatment specialists, and directors of treatment programs. A questionnaire is sent quarterly to each key informant requesting information on cases of abuse of or addiction to any of the RADARS[®] System Monitored Opioids Panel.
2. The Drug Diversion Signal Detection System – James Inciardi, Ph.D. (Univ. Delaware). This system regularly surveys more than 300 diversion investigators from jurisdictions in all 50 states, Puerto Rico and the Virgin Islands to report data on the drugs that are diverted in their jurisdictions, as determined by interdiction efforts and undercover buys.
3. The Opioid Treatment Center Signal Detection System – Mark Parrino, M.P.A. (AATOD). This includes a convenience sample of 75 methadone maintenance treatment programs that ask patients entering treatment to complete an anonymous questionnaire which inquires about the patient's drug use in the past month, lifetime drug abuse, the age when drug use first occurred, and the primary source of the abused drug(s). Results from more than 15,000 individuals nationwide have been collected and analyzed.
4. The Poison Center Signal Detection System – Richard Dart, M.D., Ph.D. (Univ. of Colorado & Rocky Mountain Poison and Drug Center). This network includes 43 of 60 poison centers representing more than 200 million people in the U.S. The poison centers provide weekly data on cases of prescription drug abuse and misuse.

8.5.2.2. Signal Verification and Evaluation

When data from any of the 4 signal detection studies indicate that there is a problem (five or more cases per 100,000 population or 2 or more cases per 100,000 population from Poison Control) in a given location (3-digit ZIP Code), field researchers trained in the use of a structured data collection instrument contact the

individuals from whom the signal information was collected and verify the signal and characterized the nature of the problem. Typically others in the area are also be contacted, with an effort to speak to at least one law enforcement officer, one substance abuse treatment professional and one pharmacist in the region. A data collection form is used that provides consistency of information obtained in these interactions. Signal verification may include phone contact or, rarely, visits to appropriate areas as part of the verification activities.

The information collected during these activities is presented to an internal Purdue Risk Intervention & Minimization Committee at scheduled meetings for evaluation and recommendations for further actions.

8.5.2.3. Focused Studies

When signal verification indicates that a significant problem exists in a given area, the RADARS[®] System SAB may recommend the development and implementation of a more focused study in that area to determine the nature and the extent of the problem so that appropriate and specific interventions can be developed. Three such studies have been completed for OxyContin[®].

OxyContin[®] Use, Abuse, and Diversion in Southwest Virginia – Janet Knisely, Ph.D. (Virginia Commonwealth University). This study involved in-depth evaluation of the local outbreak of OxyContin[®] abuse in southwest Virginia. The study included approximately 300 structured interviews of drug abusers, drug treatment personnel, law enforcement personnel, pain specialists and incarcerated drug abusers. These data provide an important historical perspective on the origin and scope of OxyContin[®] abuse in this region. This has been submitted for publication.

Illicit Opiate Use in Maine – Robert Heimer, Ph.D. (Yale University). This was an ethnographic study of opiate abuse in two counties in Maine (Washington and Cumberland) where there has been significant abuse of OxyContin[®] and other prescription drugs. The study included interviews with opioid abusers and key stakeholders in the two counties using a respondent driven sampling technique. Data collection in Cumberland County is completed. Problems were encountered in data collection in the more rural Washington County. A paper describing this work has recently been accepted for publication.

As a demonstration of the flexibility of the RADARS[®] System approach to the ever-changing landscape of prescription drug abuse, the preliminary findings in the Maine study showed an increased incidence of methadone abuse that has resulted in the addition of methadone to the RADARS[®] System drugs.

Prescription Drug Abuse in Eastern Kentucky – Carl Leukefeld, Ph.D. (University of Kentucky). This study initiated in 2004 and involved investigation into the historical and current problem of prescription drug abuse in eastern Kentucky, comparing areas of high and low prescription drug abuse. One paper from this has been published and another has been submitted for publication.⁵

8.5.3. Interventions

Data from the signal verification and focused studies are presented to the RADARS[®] System SAB for evaluation to advise on what interventions, if any, should be initiated to address the problems in that area. The following examples are potential interventions that may be implemented in specific instances. The interventions will not be limited to these, but may include these and others:

- Medical education emphasizing proper patient evaluation, selection, treatment and techniques to combat drug diversion secondary to improper prescribing of medication
- Reinforcement of good promotional practices for sales representatives
- Auditing of promotional practices
- Reporting to appropriate authorities if there are drug diversion activities identified in a specific area

8.5.3.1. Determine Effectiveness of Interventions

The RADARS[®] System SAB will continue to monitor the abuse, addiction and diversion of drugs in the specific geographic area during and following the implementation of interventions. A positive outcome of an intervention will be a decrease in signal levels in the area. If signal levels remain at a high level, further investigations will be initiated followed by additional interventions and monitoring of the outcome.

8.5.4. OTHER ACTIVITIES

- Calculation of Denominator – Raw numbers of abuse or diversion of a drug are meaningless unless they can be placed in context of the overall exposure to the drug. Therefore, it is necessary to calculate a rate for abuse and diversion. The rate of abuse for each of the RADARS[®] System drugs will be calculated using as the numerator all the unduplicated cases of abuse determined from each of the Signal Detection Studies. Various denominator candidates were explored and analyzed for their utility, including: dosage units, minimal divertable units, number of patients receiving the medication and patient-days of exposure. Currently, the denominators for reporting of rates from the Signal Detection Studies include both “patient-level data”, referred to in the RADARS[®] System as Unique Recipients of Dispensed Drugs (URDDs), to recognize the reality that not every person who receives a dispensed drug is, in fact, a patient (that is, involved in a *bona fide* prescriber-patient relationship where prescribing is for a legitimate medical purpose), and population. Both denominators are estimated at the 3-digit ZIP Code level. We have published a discussion of some of the issues inherent in choosing denominators.⁶
- Postmortem Redistribution Morphine – Patrick McKinney, M.D. and Cameron Crandall, M.D., (University of New Mexico Health Sciences Center). This protocol will study the effect of site and time on postmortem disposition of morphine in animals and humans. This work has been published.⁷
- Consulted with investigators of NIDA-funded “Monitoring the Future” survey to update the questions on prescription opioid analgesics, resulting in addition of Vicodin[®] and

OxyContin to the annual survey instrument. This change was made and reported in the 2002 and subsequent surveys.

- Working with CSAT to establish public/private work group on prescription drug abuse. Attendance at two meetings held for industry by CSAT (“Open Dialogue” Meeting I & II).

8.6. Interventions for OxyContin® Tablets

If a signal suggesting new or changing abuse or diversion of OxyContin® Tablets emerges, the following steps may be taken.

- For instances in which a specific population appears to be at risk, medical education efforts will be supplemented with public-service education targeted to the appropriate populations.
- For instances of abuse involving criminal diversion and trafficking, Purdue Pharma L.P. will
 - Provide support for law enforcement in undercover operations in affected areas;
 - Work with law enforcement to determine whether the incident involved the distribution of counterfeit OxyContin® Tablets;
 - Work with investigators to identify sources of diversion and to develop methods to reduce the diversion activities.

8.7. Other Steps Taken to Reduce the Abuse and Diversion of OxyContin®

8.7.1. Suspension of Marketing of the 160-mg Tablet

Distribution of the 160-mg tablet of OxyContin® has been voluntarily suspended. This measure was taken to reduce the risk of overdose accompanying the abuse of this dosage strength by novice drug abusers.

8.7.2. Development of Unique Indicia for OxyContin®

Unique indicia were developed for OxyContin® Tablets that distinguish OxyContin® intended for distribution in Mexico (and some countries in Latin America and South America) and Canada from OxyContin® intended for distribution in the United States. These indicia will assist law enforcement in identifying OxyContin® that has been diverted from legitimate medical channels and smuggled into the United States. In addition, sales of OxyContin® Tablets to Mexico have been suspended since December, 2001.

8.7.3. Distribution of Tamper-Resistant Prescription Pads

As one means of sensitizing prescribers to the issues of alteration or forgery of prescriptions for controlled substances, Purdue has distributed tamper-resistant prescription pads to physicians in 33 States and the District of Columbia, beginning in 2001. As of 1 October

2006, a total of 13.5 million prescription blanks have been distributed among 16,510 physicians.

9. REFERENCES

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1. PACKAGE INSERT

OXYCONTIN®

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS CII
10 mg 20 mg 40 mg 80 mg* 160 mg*

*** 80 mg and 160 mg for use in opioid-tolerant patients only**

OT00367J

300514-0G

WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

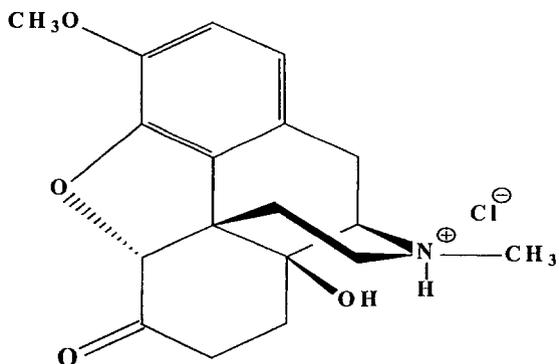
OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

OxyContin[®] (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths 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:



$C_{18}H_{21}NO_4 \cdot HCl$

MW 351.83

The chemical formula is 4, 5 α -epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder 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 tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin.

The 10 mg tablets also contain: hydroxypropyl cellulose.

The 20 mg tablets also contain: polysorbate 80 and red iron oxide.

The 40 mg tablets also contain: polysorbate 80 and yellow iron oxide.

The 80 mg tablets also contain: FD&C blue No. 2, hydroxypropyl cellulose, and yellow iron oxide.

The 160 mg tablets also contain: FD&C blue No. 2 and polysorbate 80.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

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 play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct 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 darkness. 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 OxyContin[®] overdose (See **OVERDOSAGE**).

Gastrointestinal Tract And Other Smooth Muscle

Oxycodone causes a reduction in motility 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 pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration – Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall “drug effect”, analgesia and feelings of “relaxation”.

As with all opioids, the minimum effective plasma concentration for analgesia 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 individualized 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 Experience Relationships

OxyContin[®] Tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of OxyContin Tablets is primarily due to the parent drug oxycodone. OxyContin Tablets are designed to provide controlled delivery of oxycodone over 12 hours.

Breaking, chewing or crushing OxyContin Tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OxyContin Tablets is pH independent. Oxycodone is well absorbed from OxyContin Tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin[®] was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone 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. In normal volunteers, the $t_{1/2}$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin Tablets exhibit a biphasic absorption pattern with two apparent absorption half-lives of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone by Time

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from OxyContin[®], steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin Tablets. In a study comparing 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 C_{max} , and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin Tablets than for the immediate-release formulation.

Plasma Oxycodone By Time

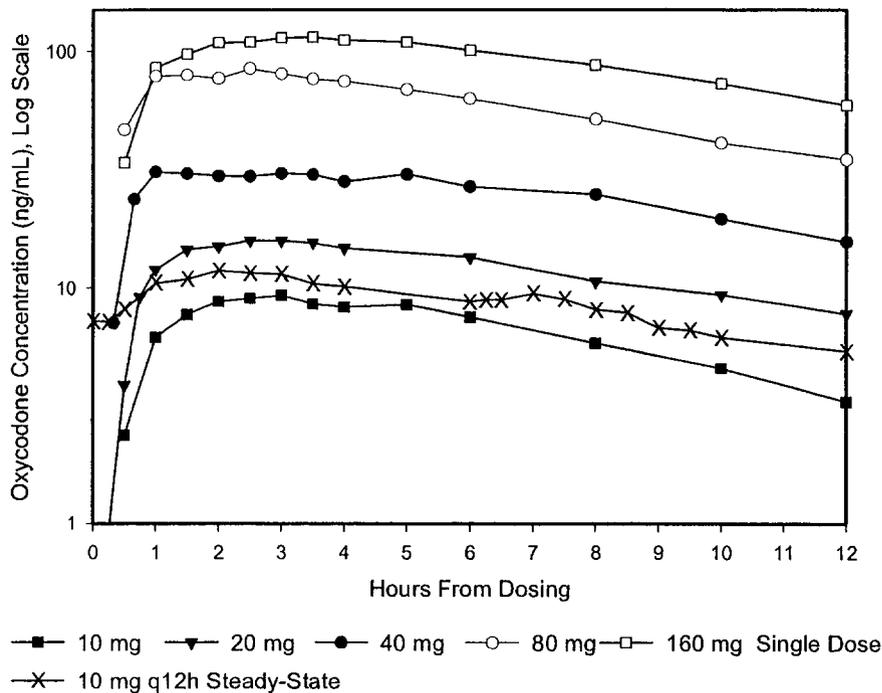


TABLE 1

Mean [% coefficient variation]

Regimen	Dosage Form	AUC (ng•hr/mL)†	C _{max} (ng/mL)	T _{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

TABLE 2

Mean [% coefficient variation]

Regimen	Dosage Form	AUC _∞ (ng•hr/mL)†	C _{max} (ng/mL)	T _{max} (hrs)	Trough Conc. (ng/mL)
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Single Dose	4 x 40 mg OxyContin*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg OxyContin*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
	1 x 160 mg OxyContin*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† for single-dose AUC = AUC_{0-inf}; for multiple-dose AUC = AUC_{0-T}

* data obtained while volunteers received naltrexone which can enhance absorption

OxyContin® is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that OxyContin Tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when a OxyContin 160 mg Tablet was administered with a high-fat meal.

Distribution

Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding 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 **PRECAUTIONS**).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).

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, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone 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 $t_{1/2}$ elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).

Drug-Drug Interactions (see **PRECAUTIONS**)

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OxyContin[®] (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of OxyContin were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of

analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

CLINICAL TRIALS

A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg OxyContin q12h but not 10 mg OxyContin q12h decreased pain compared with placebo, and this difference was statistically significant.

INDICATIONS AND USAGE

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for HealthCare Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

OxyContin[®] is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR

CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

OxyContin[®] is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

“Drug-seeking” behavior is very common in 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 referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in 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.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin[®], as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin may cause severe hypotension: There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin[®] is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Postoperative Use

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving OxyContin[®] Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or

upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin[®] without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin[®], may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo

bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects - Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

OxyContin[®] is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **PHARMACOKINETICS AND METABOLISM**). Of the total number of subjects (445) in clinical studies of OxyContin, 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 unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-

tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

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. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, 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.

ADVERSE REACTIONS

The safety of OxyContin[®] was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. 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 approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

TABLE 3

	OxyContin (n=227)	Immediate-Release (n=225)	Placebo (n=45)
	(%)	(%)	(%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	-
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in OxyContin[®]-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain, and symptoms associated with either an anaphylactic or anaphylactoid reaction

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin[®], by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCONTIN IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCONTIN® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One OxyContin 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

Patients who are not currently taking opioid analgesics should generally be started on the lowest appropriate dose (see DOSAGE AND ADMINISTRATION: Initiation of Therapy).

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM**). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see **BOXED WARNING**).

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

- (1) the general condition and medical status of the patient;
- (2) the patient's opioid exposure and opioid tolerance (if any);
- (3) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;
- (4) the reliability of the conversion estimate used to calculate the dose of oxycodone;
- (5) special safety issues associated with conversion to OxyContin[®] doses at or exceeding 160 mg q12h (see **Special Instructions for OxyContin 80 mg and 160 mg Tablets**); and
- (6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

Experience indicates a reasonable starting dose of OxyContin for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. OxyContin should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

For initiation of OxyContin therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.
3. Round down to a dose which is appropriate for the tablet strengths available.
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 4.**Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone***

	(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)	
	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	--
Codeine	0.15	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* To be used only for conversion to oral oxycodone. 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.

In all cases, supplemental analgesia should be made available in the form of a suitable short-acting analgesic.

OxyContin® can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the

patient, treatment with antiemetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin[®] may pass an intact matrix “ghost” in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family.

Special Instructions for OxyContin 80 mg and 160 mg Tablets (For use in opioid-tolerant patients only.)

OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One OxyContin[®] 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

Supplemental Analgesia

Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with OxyContin Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from OxyContin to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

OxyContin[®] (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-100-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin[®] (oxycodone hydrochloride controlled-release) Tablets 20 mg are round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-103-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin[®] (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-105-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin[®] (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other. They are supplied as follows:

NDC 59011-107-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-107-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin[®] (oxycodone hydrochloride controlled-release) Tablets 160 mg are caplet-shaped, unscored, blue-colored, convex tablets imprinted with OC on one side and 160 on the other. They are supplied as follows:

NDC 59011-109-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-109-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

CAUTION

DEA Order Form Required.

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**Purdue Pharma L.P.
Stamford, CT 06901-3431**

U.S. Patent Numbers 5,266,331; 5,508,042; 5,549,912; and 5,656,295

January 15, 2007

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PATIENT INFORMATION

OXYCONTIN® CII (Oxycodone HCl Controlled-Release) Tablets

OxyContin® Tablets, 10 mg
OxyContin® Tablets, 20 mg
OxyContin® Tablets, 40 mg
OxyContin® Tablets, 80 mg
OxyContin® Tablets, 160 mg

Read this information carefully before you take OxyContin® (ox-e-CON-tin) tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if OxyContin is right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About OxyContin®?

- **Use OxyContin the way your doctor tells you to.**
- **Use OxyContin only for the condition for which it was prescribed.**
- **OxyContin is not for occasional (“as needed”) use.**
- **Swallow the tablets whole.** Do not break, crush, dissolve, or chew them before swallowing. OxyContin® works properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep OxyContin® out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.

- **Prevent theft and misuse.** OxyContin contains a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What is OxyContin®?

OxyContin® is a tablet that comes in several strengths and contains the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. OxyContin treats moderate to severe pain that is expected to last for an extended period of time. Use OxyContin regularly during treatment. It contains enough medicine to last for up to twelve hours.

Who Should Not Take OxyContin®?

Do not take OxyContin® if

- your doctor did not prescribe OxyContin® for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 - 24 hours ago and you were not taking OxyContin just before surgery.

Your doctor should know about all your medical conditions before deciding if OxyContin is right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking OxyContin.

If you are pregnant or plan to become pregnant, talk with your doctor. OxyContin may not be right for you. **Tell your doctor if you are breast feeding.** OxyContin will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with OxyContin, especially if they cause drowsiness.

How Should I Take OxyContin®?

- **Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take OxyContin more often than prescribed.
- **Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing.** If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.
- **If you miss a dose**, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose**, call your local emergency number or Poison Control Center right away.
- **Review your pain regularly with your doctor** to determine if you still need OxyContin.
- **You may see tablets in your stools (bowel movements).** Do not be concerned. Your body has already absorbed the medicine.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping OxyContin. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking OxyContin all at once if you have been taking it for more than a few days.

After you stop taking OxyContin, flush the unused tablets down the toilet.

What Should I Avoid While Taking OxyContin®?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. OxyContin can make you sleepy.
- **Do not drink alcohol while using OxyContin.** It may increase the chance of getting dangerous side effects.
- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of OxyContin®?

Call your doctor or get medical help right away if

- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of OxyContin® are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using OxyContin.

These are not all the possible side effects of OxyContin. For a complete list, ask your doctor or pharmacist.

General Advice About OxyContin

- Do not use OxyContin for conditions for which it was not prescribed.
- Do not give OxyContin to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about OxyContin. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about OxyContin that is written for health professionals.

Rx Only

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