# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: 20-553/S-022

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-553/S-022

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Beth Connelly
Senior Regulatory Associate, U.S. Regulatory Affairs

Dear Ms. Connelly:

Please refer to your supplemental new drug application dated December 5, 2000, received December 6, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OxyContin (oxycodone hydrochloride) 10, 20, 40, 80, and 160 mg Tablets.

We also refer to your amendments to the supplement, dated April 30, June 7, June 18, June 22, June 27, and July 12, 2001, and your meetings with the Agency on April 23, June 14, and July 16, 2001.

This supplemental new drug application provides for changes to the label that address the abuse, misuse and diversion of OxyContin.

We have completed the review of this supplemental application, as amended, and it is approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-553/S-022." Approval of this submission by FDA is not required before the labeling is used.

We acknowledge your agreement to issue a Dear Health Care Provider letter and to implement a focused Communication Plan regarding the changes added to the package insert regarding these findings and the Dear Health Care Provider letter.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final

print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

*{See appended electronic signature page}*

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 20-553/S-022

## FINAL PRINTED LABELING

OxyContin®

CII

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

PACKAGE INSERT

10 mg 20 mg 40 mg 80 mg* 160 mg*
*80 mg and 160 mg for use in opioid-tolerant patients only

**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.**

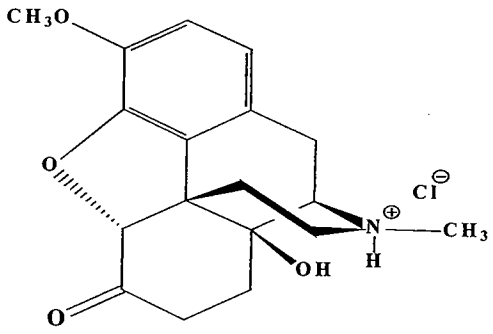
**OxyContin® 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY.** These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

**OxyContin® (oxycodone hydrochloride controlled-release) 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**

PACKAGE INSERT

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-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, hydroxypropyl methylcellulose, lactose, magnesium stearate, povidone, red iron oxide (20 mg strength tablet only), stearyl alcohol, talc, titanium dioxide, triacetin, yellow iron oxide (40 mg strength tablet only), yellow iron oxide with FD&C blue No. 2 (80 mg strength tablet only), FD&C blue No. 2 (160 mg strength tablet only) and other ingredients.

## CLINICAL PHARMACOLOGY

### Central Nervous System

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 affect 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® (oxycodone hydrochloride controlled-release) tablets is primarily due to the parent drug oxycodone. OxyContin® tablets are designed to provide controlled delivery of oxycodone over 12 hours.

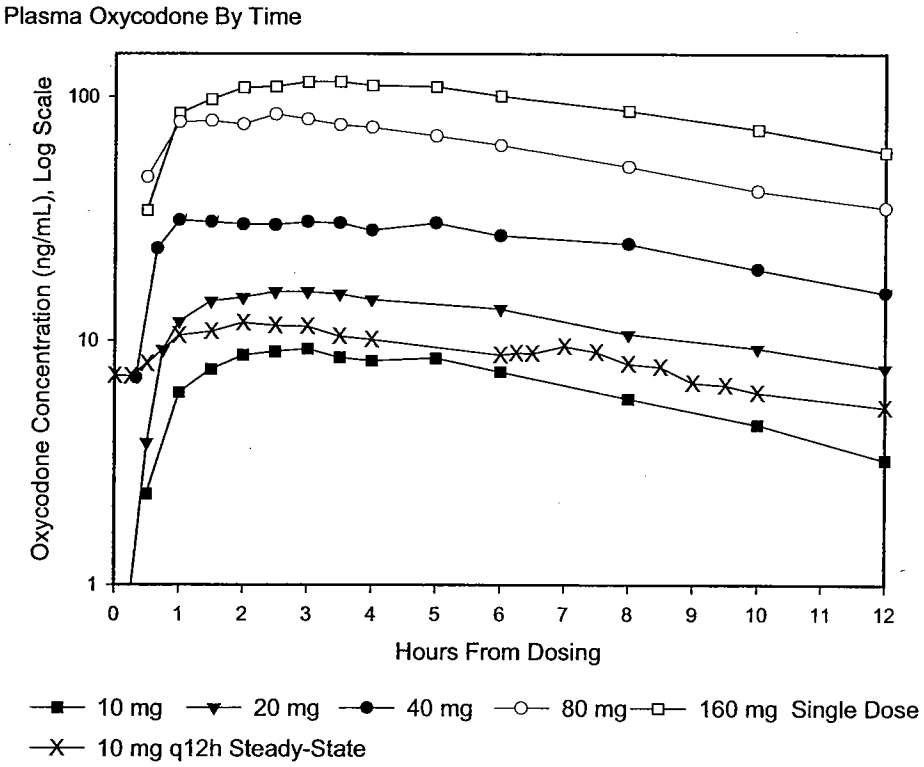
Breaking, chewing or crushing OxyContin® tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

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 t½ 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-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

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.

**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 | $AUC_{\infty}$ (ng•hr/mL)† | $C_{max}$ (ng/mL) | $T_{max}$ (hrs) | Trough Conc. (ng/mL) |
|---|---|---|---|---|---|
| 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 = $AUC_{0\text{-}inf}$; for multiple-dose AUC = $AUC_{0\text{-}T}$
* 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 OxyContin® 160 mg tablet was administered with a high fat meal.

### Distribution

Following intravenous administration, the volume of distribution (Vss) 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 t½ 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 t½ 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 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.

OxyContin® is not indicated for pain in the immediate post-operative 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 post-operative 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® (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin® TABLETS COULD LEAD TO THE 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. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

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**

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.

### 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, butorphanol, and buprenorphine) 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 Post Operative Use

**OxyContin® is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).**

**OxyContin® is not indicated for pain in the immediate post-operative 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 post-operative period if the pain is mild or not expected to persist for an extended period of time.**

**OxyContin® is only indicated for post-operative 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 post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative 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® (oxycodone hydrochloride controlled-release) 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-naive 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® (oxycodone hydrochloride controlled-release) 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 post marketing experience:

**General**: accidental injury, chest pain, facial edema, malaise, neck pain, pain

**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 overdosage 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 overdosage, 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®(oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin® TABLETS LEADS TO THE 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).**

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 requiring treatment with a strong opioid for continuous, around-the-clock analgesia 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. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring [See **BOXED WARNINGS**].

**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 daily dose, potency, and kind of the analgesic(s) the patient has been taking;
(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;
(4) the patient's opioid exposure and opioid tolerance (if any);
(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**).

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.

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.

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 (10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablets).

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 (see below) 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 anti-emetics 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 health-care 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® (oxycodone HCl controlled-release) 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) 10 mg tablets are round, unscored, white-colored, convex tablets bearing the symbol 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** 59011-100-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) 20 mg tablets are round, unscored, pink-colored, convex tablets bearing the symbol 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** 59011-103-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) 40 mg tablets are round, unscored, yellow-colored, convex tablets bearing the symbol 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** 59011-105-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) 80 mg tablets are round, unscored, green-colored, convex tablets bearing the symbol 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** 59011-107-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) 160 mg tablets are caplet-shaped, unscored, blue-colored, convex tablets bearing the symbol 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** 59011-109-25: unit dose packaging with 25 individually numbered tablets per card; one card 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.**

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

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U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295

April 25, 2001

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 20-553/S-022

## ADMINISTRATIVE DOCUMENTS

## Division of Anesthetic, Critical Care, and Addiction Drug Products

# PROJECT MANAGER LABELING REVIEW

**Application Number:** NDA 20-553/FA-022

**Name of Drug:** OxyContin (oxycodone HCL) 10, 20, 40, 80, 160 mg Tablets

**Sponsor:** Purdue Pharma L.P.

## Material Reviewed:

FA-022, dated August 17, 2001, compared with the July 18, 2001, SLR-022 approval letter with draft labeling attached.

## Review

There are several discrepancies between the approved draft labeling and the final printed labeling due to errors in the final version of the draft labeling attached to the approval letter. The submitted final printed labeling for SLR-022, however, is identical to that agreed upon in labeling negotiations and approved on July 18, 2001.

## Conclusions

The final printed labeling for SLR-002, dated August 17, 2001, received August 20, 2001, may be acknowledged and retained.

Lisa E. Basham
Regulatory Project Manager

Supervisory Comment/Concurrence:

Cathie Schumaker
Chief, Project Management Staff

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Lisa Basham
8/30/01 10:43:07 AM
CSO

for your concurrence

Cathie Schumaker
8/30/01 11:27:48 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

**Division of Anesthetic, Critical Care, and Addiction Drug Products**

**REGULATORY PROJECT MANAGER REVIEW:**

**Application Number**: NDA 20-553

**Name of Drug**: OxyContin (oxycodone HCl controlled-release) Tablets, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg.

**Sponsor**: Purdue Pharma L.P.

**RPM:** Lisa E. Basham
**Date of review:** July 18, 2001

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## PACKAGE INSERT

### Material Reviewed

| | |
|---|---|
| SLR-011 | dated August 5, 1999, received August 9, 1999 |
| SLR-021 | dated November 13, 2000, received November 14, 2000 |
| SLR-022 | dated December 5, 2000, received December 6, 2000 |
| SLR-022 BL | dated April 30, 2001, received May 1, 2001 |
| SLR-022 BL | dated June 7, 2001, received June 8, 2001 |
| SLR-022 BL | dated June 18, 2001, received June 20, 2001 |
| SLR-022 BL | dated June 27, 2001, received June 28, 2001 |
| SLR-022 BL | dated July 12, 2001, received July 16, 2001 |

**Background and Summary Description**:

In accordance with 21 CFR 314.70(b), the sponsor submitted SLR-011, dated August 5, 1999 [CBE labeling changes to the package insert to comply with 21 CFR 201.57(f)(10)(iii)(A), (Geriatric Use)], SLR-021, dated November 13, 2000 [CBE-30 labeling changes to the package insert that "add or strengthen a contraindication, warning, precaution, or adverse reaction", according to 21 CFR 314.70(c)(2)(i)], and SLR-022, dated December 5, 2000 [CBE labeling changes to the package insert that "add or strengthen a contraindication, warning, precaution, or adverse reaction", according to 21 CFR 314.70(c)(2)(ii)]. Due to concern over growing abuse, misuse and diversion of OxyContin tablets, the entire package insert was revised through a series of negotiations with the sponsor which included meetings (April 23, June 14, and July 16, 2001) and

labeling amendments to S-022 (see above). See Dr. Cynthia McCormick's Division Director's Review, dated July 16, 2001, for an overview, and the approval letter for S-022, dated July 18, 2001, for final agreed upon labeling.

Note: Agency proposed changes for S-002, submitted December 9, 1996, that were not incorporated into final labeling of the same or subsequent submissions and changes proposed in the pharmacology/toxicology review of SCS-006, but not included in the approval letter to the sponsor, were addressed during the negotiations and modified to the Agency's and the sponsor's satisfaction.

**Summary:** S-011, and S-021, are superseded by S-022 and may be acknowledged and retained. Supplement 022 has been approved based on agreed upon labeling.

Consumer Safety Officer/Lisa E. Basham

Supervisory Comment/Concurrence/Cathie Schumaker

APPEARS THIS WAY
ON ORIGINAL

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/s/
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Lisa Basham
7/18/01 03:38:32 PM
CSO

Cathie Schumaker
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CSO
Concur

APPEARS THIS WAY
ON ORIGINAL

**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

**HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857**
**Tel:(301) 827-7410**

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**Division Director's Review of Labeling Supplement and Basis for Action**

**Date:** July 16, 2001

**DRUG:** OxyContin® 10,20, 40, 80,160mg. (oxycodone hydrochloride) Controlled-Release Tablets

**Sponsor:** Purdue Pharma, L.P.

**Submission:** NDA# 20-553 SLR-022

**Subject:** Labeling Supplement—new Warnings

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*Background*

The abuse and diversion of prescription drugs has become a significant public health issue in the United States. OxyContin has been the subject of such a public health crisis. Oxycodone, the drug substance in OxyContin, is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Reports of illegal misuse, abuse, and diversion of OxyContin®, from various parts of the country have been received. These reports prompted Purdue Pharma L.P. submit a labeling supplement to the FDA on December 5, 2000 which proposed the change of the sentence [redacted]

Upon review of the labeling in the context of increased reports on abuse, addiction, death (sources include OCI (FDA) reports, DEA reports, DAWN (SAMHSA) data, and medical examiner reports) it was clear that more extensive labeling changes as well as accompanying informational messages were needed. Work began with the sponsor to strengthen the prescribing information, specifically with enhanced warnings about addiction, clarification of the drug's

therapeutic role, and additional strengthening of the Drug Abuse sections. WARNINGS were added, including a new Box Warning, which call attention to the potential for misuse, abuse and diversion and INDICATIONS were simplified to reinforce the appropriate patient population for whom this product is intended.

While OxyContin is listed in schedule II (CII) under the Controlled Substances Act, the controls have not been sufficient to stem the abuse and diversion.

The restrictions that apply to this product by virtue of the CII status will automatically include:

- Registration and separate recordkeeping of manufacture purchase and sales order forms for distribution, manufacturing quotas and security restrictions, reports to the DEA by the manufacturer and distributor. The manufacturer must submit periodic reports of the bulk drug substance and quantity of dosage forms. DEA limits the quantities of Schedule II substances which may be produced in the US in any given calendar year.
- Distributor must report the quantity and form of all transactions.
- Prescriptions can have no refills.
- A practitioner may dispense controlled substances by direct administration, by prescription or by dispensing from office supplies. Records must be maintained by the practitioner of all dispensing of controlled substances from office supplies and of certain administrations.
- Any person who handles a controlled substance must have a DEA registration.

The final agreed upon revised and approved labeling for OxyContin Tablets contains the following changes to WARNINGS and INDICATIONS.

The following BOX WARNING has been added:

**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® (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin® TABLETS LEADS TO A RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**

This is also reinforced in WARNINGS.

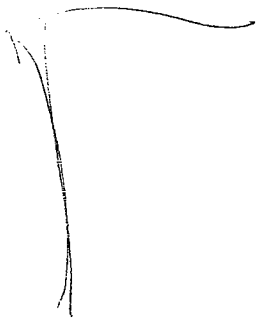
The INDICATIONS AND USAGE section now reads:

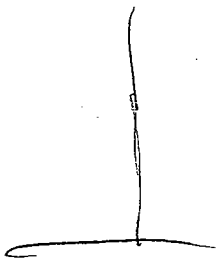
OxyContin® tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin® is not intended [redacted] for use as a prn analgesic.

***The Risk Management Program (RMP)***

The management of potential public risk has become a priority with this product, which has been shown to have a wide distribution and a growing history of diversion and abuse. The Sponsor was asked to develop a risk management plan to NDA 20-553 in March of 2001. A staged process was considered most feasible and one that would allow for immediate corrective steps. The elements of the program conceptually fall into two categories—prevention and surveillance with feedback. These are described briefly below:





***Conclusions:***

The willingness on the part of the Sponsor to consider the FDA's concerns about the development of a Risk Management Program (RMP), including an extensive educational program as its cornerstone, should be a big step towards providing adequate balance between access to this product by patients suffering with chronic pain and the prevention of collateral harm to the more widespread community by virtue of diversion and abuse. OxyContin will not likely be a viable product if the if the sponsor is unable to implement effective safeguards against the harm to individuals and communities where there has been widespread availability.

***Action:***
Approval of Labeling Supplement with Sponsor's Agreement to Implement a Risk Management Program as outlined in this review.

FDA will issue a Talk Paper to coincide with the issuance of the Dear HealthCare Provider letter.

Cynthia G. McCormick, MD
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
ODE II, CDER, FDA

July 16, 2001

APPEARS THIS WAY
ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

---

Cynthia McCormick
7/16/01 09:55:03 PM
MEDICAL OFFICER

OR ORIGINAL

PURDUE

**Purdue Pharma L.P.**
*One Stamford Forum*
*Stamford, CT 06901-3431*
*(203) 588 8000*
*Fax (203) 588 8850*
*www.purduepharma.com*

ORIGINAL

July 12, 2001

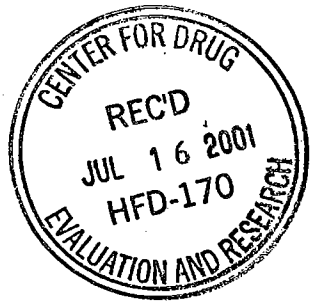
Via Federal Express

SUBMITTED IN DUPLICATE

**DRAFT PACKAGE INSERT**

NDA SUPP AMEND

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857




**Re: OxyContin® Controlled-Release Tablets**
**(oxycodone hydrochloride)**
**NDA #20-553/S-022**

Dear Dr. McCormick:

Reference is made to Purdue Pharma L.P.'s ["PPLP"] New Drug Application, NDA #20-553, for OxyContin® (oxycodone hydrochloride) Controlled-Release Tablets. We also refer to the proposed package insert changes received via e-mail on July 11, 2001.

We have reviewed the labeling and have two proposals to discuss. We would propose that the first sentence of the last paragraph of the **Indications and Usage Section** read as follows:

> OxyContin is not indicated for pain in the immediate post-operative period (the first 12-24 hours following surgery), or if the pain is mild, or... (*Rest remains the same*)

We have changed the next to last paragraph of the **Misuse, Abuse and Diversion of Opioids** section to read as follows:

> Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain is reported to be rare. However, data are not currently available to establish the true incidence of addiction in chronic pain patients.

Our belief is that the development of addiction in properly managed patients is a rare event and the rate of that event has not changed. While there may be increasing reports of overdose, criminal abuse and diversion, Purdue has not received an increasing number of reports of properly managed patients becoming addicted.

Cynthia McCormick, M.D.
OxyContin® Tablets
NDA #20-553/S-022
July 12, 2001

A revised package insert is attached.

During our teleconference on July 11, you requested a plan for educating the sales force and providing physicians with additional information on these labeling changes. We have discussed this and would propose that the [redacted]

We will try to give you our comments on the "Dear Dr." letter sometime tomorrow. With respect to that letter, we note that you have deleted [redacted] We, of course, are not wedded to the language we proposed but would like to understand the way in which FDA will communicate this request, for example, the FDA talk paper suggested by Dr. Jenkins.

If you should have any questions or comments, please contact me at the number(s) listed below.

Sincerely,

J. Christopher Prue, R.Ph.
Director,
U.S. Regulatory Affairs
Telephone: (203) 588-7558
Facsimile: (203) 588-6229

attachments

full copy to: Lisa Basham, Project Manager, HFD-170

# OXYCODONE HYDROCHLORIDE
# CONTROLLED RELEASE TABLETS

OxyContin® Tablets

Draft PACKAGE INSERT

APPEARS THIS WAY
ON ORIGINAL

# Draft Labeling

**Purdue Pharma L.P.**
*One Stamford Forum*
*Stamford, CT 06901-3431*
*(203) 588 8000*
*Fax (203) 588 8850*
*www.purduepharma.com*

ORIGINAL

June 27, 2001

NDA SUPP AMEND

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

SUBMITTED IN DUPLICATE

**DRAFT LABELING**


**Re: OxyContin® Controlled-Release Tablets**
**(oxycodone hydrochloride)**
**NDA #20-553**

Dear Dr. McCormick:

Reference is made to Purdue Pharma L.P.'s ["PPLP"] New Drug Application, NDA #20-553, for OxyContin® (oxycodone hydrochloride) Controlled-Release Tablets. We also refer to the revised draft package insert received by PPLP via e-mail on June 22, 2001 and our draft promotional materials delivered to you personally on June 25, 2001.

Attached is a draft of the "Dear Health Care Professional" letter that you requested. We look forward to your comments. Our proposed national distribution includes the following; all physicians, nurse practitioners and physician's assistants called on by our sales force, and all remaining general/family practitioners, internists, orthopedic specialists, oncologists and anesthesiologists. In addition the distribution includes all pharmacies in the United States.

We have reviewed the revised draft package insert with your latest comments and believe that we are close to resolution of the outstanding issues. We would like to amend the sentence still under discussion in the Misuse, Abuse and Diversion of Opioids section to read "The development of addiction to opioid analgesics in properly managed patients with pain

We await the comments from your Division and DDMAC on the draft promotional materials which you received on Monday so that we may see the impact of proposed labeling changes on our promotional materials.

We look forward to coming to an agreeable understanding on these issues in the near future. If you should have any questions or comments, please contact me at the number listed below.

Sincerely,

J. Christopher Prue, R.Ph.
Director,
U.S. Regulatory Affairs
Telephone: (203) 588-7558

attachment

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-553

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: J. Chris Prue, R.Ph.
Director, U.S. Regulatory Affairs

Dear Mr. Prue:

We acknowledge receipt of your August 17, 2001, submission containing final printed labeling in response to our July 18, 2001 letter approving your new drug application (NDA) for OxyContin (oxycodone hydrochloride controlled-release) 10, 20, 40, 80, 160 mg Tablets.

We have reviewed the labeling that you submitted in accordance with our July 18, 2001, letter and we find it acceptable.

If you have any questions, call Lisa E. Basham, Regulatory Project Manager, at 301-827-7420.

Sincerely,

*{See appended electronic signature page}*

Cathie Schumaker
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Cathie Schumaker
8/30/01 12:50:42 PM

APPEARS THIS WAY
ON ORIGINAL

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**Date:** **May 21, 2001**

**To:** Dr. Cynthia G. McCormick.
Director, Division of Anesthetic, Critical Care
and Addiction Drug Products (HFD-170)

**Through:** Dr. Deborah B. Leiderman
Director, Controlled Substance Staff (HFD-009)

**From:** Silvia N. Calderon, Ph.D.
Controlled Substance Staff (HFD-009)

**Subject:** NDA 20-553/S-022, OxyContin Controlled Release Tablets
Sponsor: Purdue Pharma L.P.- Label Revision

This memorandum responds to a consult from the Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170, with respect to the label of OxyContin™ from the controlled substances perspective. The Sponsor submitted a labeling supplement (S-022) on April 30, 2001 in response to the Agency's concerns regarding the misuse of OxyContin™.

**BACKGROUND**

At a meeting with the Sponsor on April 23, 2001, the Division of Anesthetic, Critical Care and Addiction Drug Products, expressed the need for a major label analysis and re-writing. Areas of concern under discussion included:

- Indication and characterization of the appropriate patient population.
- The inclusion of trial data in the label that did not contribute to the approved indication.
- The risks of abuse and overdose require emphasis and a black box warning was suggested.
- The morphine-like nature of oxycodone requires emphasis. [redacted]
- Information on opioid use and abuse, including warnings about the potential for abuse, dependence, and diversion should be included.

Recommendation:

Further revision of the label is recommended. From the drug abuse and controlled substances perspective, it is recommended that the label reflect the pharmacological profile of oxycodone, stressing that it is a morphine-like opioid.

The following specific changes are suggested:

1. Page 3, in the "Clinical Pharmacology" section, first paragraph, inclusion of the text in blue italics and elimination of the strikethrough text:

> 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, codeine and hydrocodone.* ~~*Pharmacological* effects o~~ *opioid agonists* include anxiolysis, euphoria, ~~feelings~~ of relaxation, *respiratory depression, constipation, miosis, and cough suppression as well as analgesia.* ~~[redacted]~~

2. Page 4, in the "Concentration - Adverse Experience Relationship" section, first paragraph inclusion of the text identified in blue italics:

> OxyContin tablets are associated with typical opioid-related. ~~[redacted]~~ adverse experiences ~~[redacted]~~

3. Page 8 and Page 18. The paragraphs describing "~~[redacted]~~ ' of the tablets should be moved to the "Pharmacokinetics and Metabolism", after Table 1.

4. Page 11, in the "WARNINGS" section the text indicated in blue italics should be included:

> **OxyContin® (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A ~~[redacted]~~ DOSE OF OXYCODONE .**

5. Page 11, in the "Hypotensive Effect" section, include the text indicated in blue italics,

   OxyContin®, ——— may cause severe hypotension ——— There is an added risk to individuals whose ability to maintain blood pressure has been compromised by depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. ——— may produce orthostatic hypotension in ambulatory patients. ——— , 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.

6. Page 12, in the "Misuse, and Diversion of Opioids", first and second paragraphs, include text indicated in blue italics,

   Oxycodone is ——— 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 ——— ———. 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.

7. Page 12, in the "Misuse, and Diversion of Opioids", third paragraph, include text indicated in italics:

   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**).

8. [redacted]

9. [redacted]

10. Page 14, in the "Tolerance and Physical Dependence" section, inclusion of the text in blue italics and elimination of the text, which is strikethrough:

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 ~~[redacted]~~ *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.

[redacted]

~~[redacted]~~ *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.

[redacted]

~~[redacted]~~ *In general opioids should not be abruptly stopped* (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

11. Page 14, in the "Information for Patients/Caregivers" section, Item number 1 should describe the pharmacological profile of oxycodone, for example:

*1. Patients should be aware that OxyContin tablets contain oxycodone, which is a morphine-like substance.*

12. Page 14, in the "Information for Patients/Caregivers" section, item currently numbered as 1, should include the text indicated in italics,

    Patients should be advised that OxyContin tablets were designed to work properly only if swallowed whole.

13. Page 20, in the "Drug Abuse And Addiction" section, inclusion of the text in italics and elimination of the text, which is strikethrough:

    OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule **II** controlled substance. Oxycodone,

    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 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 tru and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

    OxyContin® *like other opioids has been diverted* 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.

14. Page 25 and 26, modification of the first paragraph, to include the text in blue italics and to eliminate the text, which is strikethrough:

APPEARS THIS WAY
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Corinne Moody
5/23/01 04:08:19 PM
CSO

Deborah Leiderman
5/25/01 12:23:51 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

PURDUE

NDA NO. 20-553 REF. NO. 22
NDA SUPPL FOR SLR

**Purdue Pharma L.P.**
*One Stamford Forum*
*Stamford, CT 06901-3431*
*(203) 588 8000*
*Fax (203) 588 8850*
*www.purduepharma.com*

December 5, 2000

Via Federal Express

SUBMITTED IN DUPLICATE

**SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED - REVISED PACKAGE INSERT**

Desk Copy (Cover Letter only) to
Lisa Basham, Project Manager

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC - 6 2000
HFD-170

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

**Re: OxyContin® 10, 20, 40, 80 and 160 mg Controlled-Release Tablets**
**NDA #20-553**

Dear Dr. McCormick:

Please refer to our New Drug Application, NDA #20-553 for OxyContin® (oxycodone hydrochloride) Controlled-Release Tablets.

[redacted]

We are herein submitting a second "Special Supplement: Changes Being Effected - Revised Package Insert" which provides for a change that "add(s) or strengthen(s) a statement about drug abuse, dependence, or overdosage" in accordance with 21 CFR §314.70(c)(2)(ii). This change is located on Page 19 in the DRUG ABUSE AND DEPENDENCE (ADDICTION) section:

Cynthia McCormick, M.D.
OxyContin® 10, 20, 40, 80 and 160 mg Controlled-Release Tablets
NDA #20-553
December 5, 2000

| **Current Text:** | **Proposed Revised Text (new wording is italicized):** |
|---|---|
| [ ] | [ ] |
| [ ] | [ ] |

[ ] [ ]

[ ] To avoid any such misunderstanding, Purdue is initiating the revision defined herein.

The attached package insert (N4909 dated **November 27, 2000**) is in redline/strikeout format to show the changes. Final printed labeling will be submitted to the Agency once available.

A completed User Fee Cover Sheet (Form FDA 3397) is also attached.

If you require any further information, please contact me at the number(s) listed below.

Sincerely,

Beth Connelly

Beth Connelly
Senior Regulatory Associate,
U.S. Regulatory Affairs
Telephone: (203) 588-7289
Facsimile: (203) 588-6229

APPEARS THIS WAY
ON ORIGINAL

BC:jmm
attachments

PURDUE

**Purdue Pharma L.P.**
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**NDA SUPP AMEND**
ORIGINAL

April 30, 2001

Via Federal Express

SUBMITTED IN DUPLICATE

**GENERAL CORRESPONDENCE:**
**DRAFT PROPOSED PACKAGE INSERT**
**(S-022)**


Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

**Re: OxyContin® 10, 20, 40, 80 and 160 mg**
**Controlled-Release Tablets**
**NDA #20-553/S-022**

Dear Dr. McCormick:

Please refer to our New Drug Application, NDA #20-553 for OxyContin® (oxycodone hydrochloride) Controlled-Release Tablets.

Reference is also made to the April 23, 2001 meeting to discuss the abuse and diversion of OxyContin® tablets and to the Agency's request to formally submit our recommendations for package insert revisions which address these issues. It was agreed that these recommendations would be submitted under the open labeling supplement S-022.

Herein are hard copies of the package insert, an annotated (redline/strikeout) version to show the proposed revisions as well as a clean version, which contain our proposed amended language intended to address the issues of drug abuse and diversion.

If you require any further information, please contact me at the number(s) listed below.

Sincerely,

J. Christopher Prue, R.Ph., MBA
Director, U.S. Regulatory Affairs
Telephone: (203) 588-7558
Facsimile: (203) 588-6229

BC:jmm
enclosure

copy (cover letter only) to: Lisa Basham, Project Manager
FDA, Division of Anesthetic, Critical Care and
Addiction Drug Products

APPEARS THIS WAY
ON ORIGINAL

**PURDUE**

**Purdue Pharma L.P.**
*One Stamford Forum*
*Stamford, CT 06901-3431*
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*www.purduepharma.com*

June 7, 2001

Via Federal Express

SUBMITTED IN DUPLICATE

DRAFT PACKAGE INSERT

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857


**Re: OxyContin® Controlled-Release Tablets**
**(oxycodone hydrochloride)**
**NDA #20-553/S-022**

Dear Dr. McCormick:

Reference is made to Purdue Pharma L.P.'s ["PPLP"] New Drug Application, NDA #20-553, for OxyContin® (oxycodone hydrochloride) Controlled-Release Tablets. We also refer to the meeting held on April 23, 2001 to discuss the drug abuse and diversion of OxyContin® and the efforts in dealing with this serious problem. It was noted in this meeting that the Agency would be recommending changes to the package insert for OxyContin® and we acknowledge receipt of the recommendations by facsimile on the evening of May 23, 2001.

Attached is PPLP's response to your recommendations in both a red-line strike out version and a clean copy of the revised text. We agree with most of the recommendations made in the May 23, 2001 document and have incorporated suggested changes in several places. Most notably we have created language in a "black box warning" and incorporated the suggested language regarding abuse, liability and diversion. Where references to data were required in order to justify specific information in the insert, we have provided those references or removed the specific information in question.

There are a few discussion points concerning this response where we believe an explanation of our rationale would be helpful to the Agency in reviewing this draft. We have included "Note to FDA" in the text of the attached draft package insert where these explanations are inserted.

As you indicated to PPLP during our meeting on April 23 (and subsequently at our May 31, 2001 meeting at the Drug Enforcement Administration), we understand it to be your intention to treat all pharmaceutical companies equally and to apply the same standards to all Schedule II and III narcotics as are being requested of PPLP. We reiterate our

willingness to voluntarily accept the "black box warning" and the proposed language on abuse, diversion and addiction, provided that FDA makes clear that these requests are not unique to OxyContin® but are being made with respect to all Schedule II and III narcotics.

We know of no data to suggest that there are differences in the addiction, abuse and diversion potential of oxycodone and other drugs of its type. The language proposed by the Agency in the "Misuse, Abuse and Diversion of Opioids" section of the package insert recognizes this. To lead prescribers and the public to believe that the new language is unique to OxyContin® Controlled-Release Tablets is to mislead and confuse them as to the risk potential of other drugs such as morphine, hydromorphone, fentanyl and hydrocodone. To be clear, we are not suggesting that we will make these changes only when they are accepted by companies with similar drugs, but rather that we are asking FDA, consistent with your comments, to request that others make similar changes to similar products.

We trust that the proposed draft package insert meets with your approval. We look forward to discussing this draft at the meeting scheduled for June 14, 2001. If you should have any questions or comments before this scheduled meeting, please contact me at the number(s) listed below.

Sincerely,

JCPrue

J. Christopher Prue, R.Ph.
Director,
U.S. Regulatory Affairs
Telephone: (203) 588-7558
Facsimile: (203) 588-6229

APPEARS THIS WAY
ON ORIGINAL

attachments

copy of cover letter only to:
Lisa Basham, Project Manager -
FDA, Division of Anesthetic, Critical Care and Addiction Drug Products

ORIGINAL

CENTER FOR DRUG
REC'D
AUG 20 2001
HFD-170
EVALUATION AND RESEARCH

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**PURDUE**

**Purdue Pharma L.P.**
*One Stamford Forum*
*Stamford, CT 06901-3431*
*(203) 588 8000*
*Fax (203) 588 8850*
*www.purduepharma.com*

August 17, 2001

NDA SUPP AMEND

Via Federal Express

SUBMITTED IN DUPLICATE

**GENERAL CORRESPONDENCE:**
**FINAL PRINTED LABELING FOR APPROVED SUPPLEMENT**
**NDA 20-553/S-022**

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Product
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

**Re: OxyContin® Tablets**
**NDA #20-553**

Dear Dr. McCormick:

Please refer to Purdue Pharma L.P.'s ("PPLP") New Drug Application #20-553 for OxyContin® Tablets approved by the Agency on December 12, 1995 and to your July 18, 2001 approval letter of a revised package insert in which the Agency requested Final Printed Labeling.

In accordance with the July 18, 2001 letter, included herein are twenty (20) copies of the Final Printed Labeling, Artwork Control #OT00367. As requested, ten (10) copies are individually mounted in plastic on heavy weight paper and the remaining ten (10) are in one plastic sleeve. The introductory promotional materials were submitted under separate cover on August 7, 2001 to the Anesthetics Division and to the Division of Drug Marketing, Advertising and Communications.

If you should have any questions, please contact me at the number(s) given below.

Sincerely,

Beth Connelly

Beth Connelly
Senior Regulatory Associate,
U.S. Regulatory Affairs
Telephone: (203) 588-7289
Facsimile: (203) 588-6229

APPEARS THIS WAY
ON ORIGINAL

BC:jmm
attachment
*copy (cover letter only) to: Lisa Basham, Project Manager,*
*FDA, Div. of Anesthetic, Critical Care & Addiction Drug Products*

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