DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 11 2000

TRANSMITTED VIA FACSIMILE

Beth Connelly, R.N.
Senior Associate
Regulatory Affairs
Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, CT 06850-3590

RE: NDA 20-553
OxyContin (oxycodone hydrochloride Controlled-Release) tablets
MACMIS ID # 8636

Dear Ms. Connelly:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified an advertisement for OxyContin (oxycodone hydrochloride Controlled-Release) tablets, disseminated by Purdue Pharma L.P. (Purdue) that violates the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, your journal advertisement entitled, "Proven Effective in Arthritis Pain," in the May 4, 2000 issue of the *New England Journal of Medicine* promotes OxyContin in a manner that is false or misleading. Our specific objections follow:

Misleading Efficacy Presentation

- You present the headline, "Proven Effective In Arthritis Pain" on the first page of the journal ad, followed by the results of a study conducted in 133 patients with moderate to severe osteoarthritis on the second page. This presentation suggests that OxyContin has been studied in all types of arthritis and can be used as first-line therapy for the treatment of osteoarthritis. However, this suggestion is unsubstantiated and lacks important information about the study. Specifically, the approved product labeling (PI) for OxyContin states, "A double-blind, placebo-controlled, fixed-dose, parallel group study was conducted in 133 patients with moderate to severe osteoarthritis pain, **who were judged as having inadequate pain control with prn opioids and maximal non-steroidal anti-inflammatory therapy**" (emphasis added). Therefore, your journal ad is misleading because it suggests that OxyContin can be used as first-line therapy for the treatment of arthritis when such has not been demonstrated by substantial evidence. In addition, the journal ad is misleading because it does not prominently present the important contextual information that the inclusion criteria for the study were patients who were judged as having inadequate pain control with prn opioids and maximal NSAID therapy.

- You present the headline, "IN A STUDY OF 133 PATIENTS WITH MODERATE TO SEVERE OSTEOARTHRITIS PAIN*," followed by bulleted claims about this study. This presentation is followed by the product logo for OxyContin along with various doses of OxyContin that are available. This presentation suggests that any dose of OxyContin can be used for the treatment of moderate to severe osteoarthritis pain. However, the study only demonstrated OxyContin 20mg given twice daily to be significantly more effective than placebo at day 7 and 14. In fact, OxyContin 10mg given twice daily was no better than placebo in reducing pain intensity. Therefore, your suggestion that any dose of OxyContin can be used in the treatment of moderate to severe osteoarthritis pain is unsubstantiated, and consequently, misleading.

Misleading Safety Presentation

- You present a picture of an elderly person on the first page of the journal ad under the headline, "Proven Effective in Arthritis Pain." Promotional materials are misleading if they promote a drug in a selected class of patients without presenting risk information especially applicable to that selected class of patients. The Warnings section of the PI states that, "Respiratory depression occurs most frequently 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." This risk is not presented in your journal ad. Therefore, the suggestion that OxyContin can be used in the elderly without prominent disclosure of the above risk information is misleading.

You should immediately discontinue the use of this journal advertisement and all other promotional materials for OxyContin that contain the same or similar claims or presentations. You should submit a written response to us on or before May 25, 2000, describing your intent and plans to comply with the above. Your letter should include a list of materials discontinued and the date on which these materials were discontinued.

You should direct your response to me by facsimile at (301) 594-6771, or by writing at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

Sincerely,

/S/

Spencer Salis, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

Proven EFFECTIVE in ARTHRITIS PAIN

PURDUE

OxyContin 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 toxic dose of oxycodone.

The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

IN A STUDY OF 133 PATIENTS WITH MODERATE TO SEVERE OSTEOARTHRITIS PAIN*

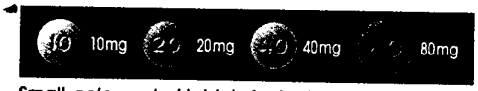
- OxyContin provided smooth and sustained pain control over a two-week period*
- All patients were dosed q12h*
- 94% of peak pain reduction was achieved by Day 3 of therapy*
- Quality of life benefits—relative to placebo, OxyContin significantly decreased pain and improved quality of life, mood, and sleep*
- Single-entity agent—contains no acetaminophen or aspirin—can be used concomitantly with NSAIDs

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

Q12h

OXYCONTIN® C II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS



Small, color-coded tablets (actual size)

OxyContin 80 mg Tablet for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more.

Prompt onset, prolonged control

In noncancer patients: A prn opioid or OxyContin may be appropriate as initial opioid therapy, as judged by the prescriber.

When initiating any opioid in opioid-naive patients, significant side effects such as dizziness, nausea, vomiting and hypotension may be seen in the first days of therapy. Most side effects with OxyContin, except constipation, diminish over time.

Please read brief summary of professional prescribing information on adjacent page.

For more information about pain management and prevention, visit our Web site: www.partnersagainstpain.com

Co-promoted by Purdue Pharma L.P. and Abbott Laboratories.

A5972

PUR4000324

*Sunshine A, Olson NZ, Colon A, et al. Analgesic efficacy of controlled-release oxycodone in postoperative pain. *J Clin Pharmacol 1996;36:595-603*

OxyContin® II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg 20 mg 40 mg 80 mg

80 mg For use in opioid tolerant patients only.

Brief Summary on OxyContin® (oxycodone hydrochloride controlled-release) Tablets.

Before prescribing, see complete prescribing information, including DOSAGE AND ADMINISTRATION

INDICATIONS AND USAGE:

For the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.

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 paralyticileus.

WARNINGS:

OxyContin® 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 TOXIC DOSE OF OXYCODONE.

Respiratory Depression

Respiratory depression, the chief hazard from all opioid agonist preparations, occurs most frequently 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 preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

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

Hypotensive Effect

OxyContin®, like all opioid analgesics, may cause severe hypotension in an individual 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. OxyContin may produce orthostatic hypotension in ambulatory patients. OxyContin, like all opioid analgesics, 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:

Special precautions regarding OxyContin® 80 mg Tablets

OxyContin® 80 mg Tablets are for use only in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescription of this tablet strength. 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.

General — OxyContin® tablets are intended for use in patients who require oral pain therapy with an opioid agonist of more than a few days duration. As with any opioid analgesic, it is critical to adjust the dosing regimen individually for each patient.

Selection of patients for treatment with OxyContin should be governed by the same principles that apply to the use of similar controlled-release opioid analgesics. Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other 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. Physicians should individualize treatment in every case, using non-opioid analgesics, prn opioids and/or combination products,and chronic opioid therapy with drugs such as OxyContin in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and the American Pain Society.

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, like all opioid analgesics, 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, like all opioid analgesics, 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

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of 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.

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 PRECAUTIONS: Drug-Drug Interactions).

Post-Operative Use

Morphine and other 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 the occurrence of 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.

Significant tolerance should not occur in most of the patients treated with the lowest doses of oxycodone. It should be expected, however, that a fraction of cancer patients will develop some degree of tolerance and require progressively higher dosages of OxyContin to maintain pain control during chronic treatment. Regardless of whether this occurs as a result of increased pain secondary to disease progression or pharmacological tolerance, dosages can usually be increased safely by adjusting the patient's dose to maintain an acceptable balance between pain relief and side effects. The dosage should be selected according to the patient's individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effect of opioids is usually paralleled by tolerance to side effects, except for constipation.

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity (see OVERDOSAGE). If OxyContin is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. This 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.

If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support.

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin should be given the following information by the physician:

1. OxyContin tablets were designed to work properly only if swallowed whole. They may release all their contents at once if broken, chewed or crushed, resulting in a risk of overdose.
2. Report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
3. Do not adjust the dose of OxyContin without consulting the prescribing professional.
4. OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
5. Do not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.
6. Women of childbearing potential who become, or are planning to become, pregnant should consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
7. OxyContin is a potential drug of abuse. Patients should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
8. Patients may pass empty matrix "ghosts" (tablets) via colostomy or in the stool; this is of no concern since the active medication has already been absorbed.
9. If patients 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.

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.

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 which cause central nervous system depression.

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 CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and 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.

Mutagenicity/Carcinogenicity

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 and with activation after 48 hours of exposure) at doses of up to 1500 µg/mL and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 µg/ml). Mutagenic results occurred 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. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Pregnancy

Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg (48 mg/m²) and 125 mg/kg (1375 mg/m²), respectively. These doses are 4 and 60 times a human dose of 120 mg/day (74 mg/m²), based on mg/kg of a 60 kg adult (0.7 and 19 times this human dose based upon mg/m²). 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.

Nonteratogenic Effects—Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

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.

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 since oxycodone may be excreted in the milk.*Pediatric Use*

Safety and effectiveness in pediatric patients below the age of 18 have not been established with this dosage form of oxycodone. However, oxycodone has been used extensively in the pediatric population in other dosage forms, as have the excipients used in this formulation. No specific increased risk is expected from the use of this form of oxycodone in pediatric patients old enough to safely take tablets if dosing is adjusted for the patient's weight. **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%. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen based on age, and the usual doses and dosing intervals are appropriate for the geriatric patient.

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.

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.

Rectal Administration

OxyContin Tablets are not recommended for administration per rectum. A study in normal volunteers showed a significantly greater AUC and higher C_{max} during this route of administration.

ADVERSE REACTIONS:

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

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.

In clinical trials comparing OxyContin with immediate-release oxycodone and placebo, the most common adverse events (>5%) reported by patients (pts) at least once during therapy were:

	OxyContin (n=227) # Pts (%)		Immediate-Release (n=225) # Pts (%)		Placebo (n=45) # Pts (%)	
Constipation	52	(23)	58	(26)	3	(7)
Nausea	52	(23)	60	(27)	5	(11)
Somnolence	52	(23)	55	(24)	2	(4)
Dizziness	29	(13)	35	(16)	4	(9)
Pruritus	29	(13)	28	(12)	1	(2)
Vomiting	27	(12)	31	(14)	3	(7)
Headache	17	(7)	19	(8)	3	(7)
Dry Mouth	13	(6)	15	(7)	1	(2)
Asthenia	13	(6)	16	(7)	—	—
Sweating	12	(5)	13	(6)	1	(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:

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: dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

DRUG ABUSE AND DEPENDENCE (Addiction):

OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

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.

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. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OxyContin®. In such cases, 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.

SAFETY AND HANDLING:

OxyContin® tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

CAUTION: DEA Order Form Required.

R_x Only.

Manufactured by The PF Laboratories, Inc., Totowa, N.J. 07512

Distributed by Purdue Pharma L.P., Norwalk, CT 06850-3590

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

June 15, 1998 G4909-BS