

PRODUCT MONOGRAPH

^NOxyContin[®]

**Oxycodone Hydrochloride Controlled Release Tablets
5, 10, 15, 20, 30, 40, 60 and 80 mg**

^NOxy•IR[®]

**Oxycodone Hydrochloride Tablets
5, 10 and 20 mg**

**Purdue Pharma Std.
Opioid Analgesic
ATC: N02AA05**

Purdue Pharma
575 Granite Court
Pickering, Ontario
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Control No.: 130746 / 130747

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NAME OF DRUG

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PHARMACOLOGICAL CLASSIFICATION

Opioid Analgesic

ACTIONS

Oxycodone is a semi-synthetic opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, oxycodone produces a variety of effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory center to CO₂, nausea and vomiting via stimulation of the chemoreceptor trigger zone, changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

Oxycodone retains at least one-half of its analgesic activity when administered orally and with acute dosing is approximately twice as potent as orally administered morphine.

Studies with **OxyContin[®]** (oxycodone hydrochloride controlled release tablets) and **Oxy•IR[®]** (oxycodone hydrochloride tablets) in normal volunteers and patients demonstrate a consistent relationship between oxycodone dosage and plasma oxycodone concentrations as well as between concentration and pharmacodynamic effects. In a single dose analgesic assay, the peak effect of **OxyContin** (20 and 30 mg) was greater than that of 10 mg **OxyContin** and was equivalent to that of two tablets of oxycodone (5 mg) plus acetaminophen (325 mg), or 15 mg of immediate release oxycodone but with a longer duration of action. In patients with pain due to osteoarthritis, **OxyContin** q12h was more effective than placebo in decreasing pain and in improving quality of life, mood and sleep. In patients with cancer pain, **OxyContin** administered q12h produced equivalent analgesia to **Oxy•IR** administered four times per day. In patients with low back pain, **OxyContin** q12h was equally effective as **Oxy•IR** given four times per day. Titration to analgesic effect was achieved as easily with **OxyContin** as with **Oxy•IR**.

There is no intrinsic limit to the analgesic effect of oxycodone; like morphine, adequate doses will relieve even the most severe pain. Clinically however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, nausea and vomiting, which can result from high doses.

Pharmacokinetics:

After oral administration, oxycodone is absorbed from the gastrointestinal tract and has a relatively high bioavailability of approximately 60 - 87%. Unlike morphine, oxycodone does not undergo high first pass metabolism, possibly due to the protective effect of a methoxy group in

the 3 position which is a site of morphine glucuronidation. Oxycodone is metabolized in the liver to noroxycodone, oxymorphone, noroxymorphone and their glucuronides. The formation of oxymorphone and noroxycodone is mediated by cytochrome P450 2D6 and its cytochrome P450 3A4, respectively. In addition, noroxymorphone formation is mediated by both cytochrome P450 2D6 and cytochrome P450 3A4. Therefore, the rate of formation of these metabolites can, in theory, be affected by other drugs (see **PRECAUTIONS**, **Drug Interactions**).

The in vitro drug-drug interaction studies with noroxymorphone using human liver microsomes resulted in no significant inhibition of CYP2D6 and CYP3A4 activities, which suggest that noroxymorphone may not alter the metabolism of other drugs that are metabolized by CYP2D6 and CYP3A4. Noroxymorphone has been shown to bind to μ -opioid receptor. Although oxymorphone has been shown to be active, the analgesic effects of the metabolites are thought to be clinically insignificant.

Oxymorphone is known to possess analgesic activity but concentrations in the plasma are very low and not as closely correlated to opioid effects as oxycodone concentrations. Although the AUC ratio of noroxycodone to oxycodone is about 0.6 following oral dosing, noroxycodone is reported to be a considerably weaker analgesic than oxycodone and is unlikely to contribute significantly to the analgesic effect of oxycodone. The analgesic activity profile of other metabolites is not known. The terminal elimination half-life after immediate release tablets is approximately 4 hours. The majority of metabolites and unchanged drug (conjugated 2.2%, unconjugated 5.5%) are excreted in the urine and feces.

Pharmacokinetic studies of **OxyContin** in normal volunteers demonstrate that both AUC and C_{max} increase in a dose proportional manner and that the six tablet strengths are bioequivalent. In single dose studies, **OxyContin** was absorbed to an equivalent extent as immediate release oxycodone but with a reduced maximum concentration (C_{max} ratio approximately 50%), a prolonged (2.4x) time to maximum concentration (t_{max} approximately 2.8 hours), with a biphasic absorption pattern, with two apparent absorption half-times of 0.6 and 6.9 hours, which describe the initial release of oxycodone from the tablet, followed by a prolonged release. Release in vitro is pH-independent. **OxyContin** tablets 15 mg, 30 mg and 60 mg are proportionally bioequivalent to **OxyContin** tablets 40 mg in terms of AUC_t , AUC_{INF} and C_{max} of oxycodone, and mean half-life values and median t_{max} values were all similar.

In steady state pharmacokinetic studies of **OxyContin** q12h, maximum plasma concentrations (C_{max}) of oxycodone were equivalent to those obtained with q6h administration of oral immediate release preparations and was achieved approximately 3 hours after administration of **OxyContin**. Steady-state was achieved within 24-36 hours of initiation of dosing. The absorption of oxycodone from **OxyContin** tablets is not significantly influenced when administered in the presence of food.

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. Plasma concentrations of oxycodone are increased by approximately 15% in elderly subjects receiving **OxyContin**; by 50 - 60% in patients with moderate degrees of renal impairment; and by approximately two-fold in patients with hepatic cirrhosis.

INDICATIONS

OxyContin[®] (oxycodone hydrochloride controlled release tablets) are indicated for relief of moderate to severe pain requiring the continuous use of an opioid analgesic preparation for several days or more.

Oxy•IR[®] (oxycodone hydrochloride tablets) are indicated for relief of moderate to severe pain.

CONTRAINDICATIONS

OxyContin[®] (oxycodone hydrochloride controlled release tablets) and **Oxy•IR[®]** (oxycodone hydrochloride tablets) should not be given to patients with: hypersensitivity to opioid analgesics; acute asthma or other obstructive airway disease and acute respiratory depression with hypoxia; elevated carbon dioxide levels in the blood; cor pulmonale; acute alcoholism; delirium tremens; severe CNS depression; convulsive disorders; increased cerebrospinal or intracranial pressure; head injury; suspected surgical abdomen (e.g., paralytic ileus); concomitant MAO inhibitors (or within 14 days of such therapy).

WARNINGS

OxyContin[®] (oxycodone hydrochloride controlled release tablets) should be swallowed whole. Taking broken, chewed, dissolved or crushed OxyContin tablets could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.

OxyContin 60 mg and 80 mg tablets, or a single dose greater than 40 mg, are for use in opioid tolerant patients only (see also DOSAGE AND ADMINISTRATION). A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids (see PRECAUTIONS, Drug Interactions).

Patients should be instructed not to give OxyContin or Oxy•IR[®] (oxycodone hydrochloride tablets) to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Patients should be cautioned not to consume alcohol while taking **OxyContin or Oxy•IR**, as it may increase the chance of experiencing dangerous side effects.

Abuse of Opioid Formulations: OxyContin consists of a dual polymer matrix intended for oral use only. Abuse can lead to overdose and death. This risk is increased when the tablets are crushed, broken, dissolved or chewed, and with concurrent consumption of alcohol or other CNS depressants. 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.

Drug Dependence: As with other opioids, tolerance and physical dependence may develop upon repeated administration of oxycodone and there is a potential for development of psychological dependence. **OxyContin** tablets and **Oxy•IR** should therefore be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential. Drug abuse is usually not a problem in patients with pain in whom oxycodone is appropriately indicated. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist.

Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

Use in Drug and Alcohol Addiction: **OxyContin/Oxy•IR** are opioids with no approved use in the management of addictive disorders. Their proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia.

CNS Depression: Oxycodone should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants and other CNS depressants,

including alcohol. Respiratory depression, hypotension and profound sedation or coma may result.

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive **OxyContin** or **Oxy•IR** within 24 hours of the procedure.

Use in Pregnancy: While animal reproduction studies have revealed no evidence of harm to the fetus due to oxycodone, safe use in pregnancy has not been established. **OxyContin** or **Oxy•IR** should be given to pregnant patients only when the anticipated benefits outweigh the potential risks to the fetus and should be avoided to the extent possible in patients who are pregnant.

PRECAUTIONS

Respiratory Depression: Oxycodone should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide (CO₂) on the respiratory centre and the respiratory depressant effects of oxycodone may reduce respiratory drive to the point of apnea.

Head Injury: The respiratory depressant effects of oxycodone, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated

intracranial pressure produced by trauma. Also, oxycodone may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, oxycodone must be used with extreme caution and only if it is judged essential.

Hypotension: Oxycodone administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines or certain anaesthetics.

Acute Abdominal Conditions: Oxycodone and other morphine-like opioids have been shown to decrease bowel motility. Oxycodone may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Special Risk Groups: Oxycodone should be administered with caution and in a reduced dosage to debilitated patients, to patients with severely reduced hepatic or renal function, and in patients with Addison's disease, hypothyroidism, toxic psychosis, pancreatitis, prostatic hypertrophy or urethral stricture.

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 postoperative period if the pain is mild or not expected to persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.

Patients who are already receiving **OxyContin** tablets as part of ongoing analgesic therapy may be continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given including perioperative medications (see **PRECAUTIONS**, **Drug Interactions**, Mixed agonist/antagonist opioid analgesics) and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**, and **PRECAUTIONS**, **Drug Interactions**).

Oxycodone 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.

OxyContin should not be used in the early post-operative period (12-24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal (see also **PRECAUTIONS**, **Drug Interactions**, Mixed agonist/antagonist opioid analgesics).

Oxy•IR should be used with caution pre-operatively and within the first 12-24 hours post-operatively.

Use during Labour/Delivery and in Nursing Mothers: In view of the potential for opioids to cross the placental barrier and to be excreted in breast milk, oxycodone use should be avoided to the extent possible in nursing mothers. Physical dependence or respiratory depression may occur in the infant if opioids are administered during labour.

Driving and Operating Dangerous Machinery: Oxycodone may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of oxycodone with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

Drug Interactions: CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, antidepressants, sleeping aids, phenothiazines, neuroleptics, chloral hydrate and glutethimide may enhance the depressant effect of oxycodone (see **PRECAUTIONS**, Ambulatory Surgery and Post-Operative Use). Oxycodone should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are currently receiving other central nervous system depressants. Monoamine oxidase inhibitors (including procarbazine hydrochloride), pyrazolidone, antihistamines, beta-blockers and alcohol may also enhance the depressant effect of oxycodone.

Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 and in theory, can be affected by other drugs. While these pathways may be blocked by a variety of drugs, such blockage has not yet been shown to be of clinical significance with this agent.

“In Vitro” Dissolution Studies of Interaction with Alcohol: Increasing concentrations of alcohol in the dissolution medium, resulted in a slight decrease in the rate of release of oxycodone from **OxyContin** tablets.

Mixed agonist/antagonist opioid 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.

ADVERSE REACTIONS

Adverse effects of **OxyContin[®]** (oxycodone hydrochloride controlled release tablets) and **Oxy•IR[®]** (oxycodone hydrochloride tablets) are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed adverse effects of **OxyContin** and **Oxy•IR** are asthenia, constipation, dizziness, dry mouth, headache, nausea, pruritus, somnolence, sweating and vomiting.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel

obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required.

The following adverse effects occur less frequently with opioid analgesics and include those reported in **OxyContin** and **Oxy•IR** clinical trials, whether related or not to oxycodone.

General and CNS: abnormal dreams, abnormal gait, agitation, amnesia, anaphylactic reaction, anaphylactoid reaction, anxiety, confusional state, convulsion, delirium, depersonalization, depression, disorientation, drug dependence, drug tolerance, drug withdrawal syndrome, dysphoria, emotional lability, euphoria, hallucinations, headache, hypertonia, hypoaesthesia, hypotonia, insomnia, miosis, muscle contractions involuntary, nervousness,

paresthesia, speech disorder, thought abnormalities, tinnitus, tremor, twitching, vertigo and vision abnormalities

Cardiovascular: chest pain, faintness, hypotension, migraine, palpitation, ST depression, syncope, tachycardia and vasodilation

Respiratory: bronchitis, bronchospasm, cough, dyspnea, pharyngitis, pneumonia, respiratory depression, sinusitis and yawning

Gastrointestinal: abdominal pain, anorexia, biliary spasm, diarrhea, dyspepsia, dysphagia, eructation, flatulence, gastritis, gastrointestinal disorder, hiccups, ileus, increased appetite, stomatitis and taste perversion

Genitourinary: amenorrhea, antidiuretic effects, libido decreased, dysuria, hematuria, impotence, polyuria, urinary retention or hesitancy

Dermatologic: dry skin, exfoliative dermatitis, edema, other skin rashes and urticaria

Other: allergic reaction, asthenia, chills, dehydration, fever, hypoglycemia, increased hepatic enzymes, lymphadenopathy, malaise, thirst and weight loss

Withdrawal (Abstinence) Syndrome: Physical dependence with or without psychological dependence tends to occur with chronic administration. An abstinence syndrome may be precipitated when opioid administration is discontinued or opioid antagonists administered. The following withdrawal symptoms may be observed after opioids are discontinued: body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal from the drug, these symptoms are usually mild.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

Symptoms: Serious overdose with oxycodone may be characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, miotic pupils, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. Severe overdose may result in apnea, circulatory collapse, cardiac arrest and death.

Treatment: Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression

due to overdosage or as a result of unusual sensitivity to oxycodone. An appropriate dose of an opioid antagonist should therefore be administered, preferably by the intravenous route. The usual initial i.v. adult dose of naloxone is 0.4 mg or higher. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of oxycodone, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

In individuals physically dependent on opioids, the administration of the usual dose of narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of narcotic antagonists in such individuals should be avoided if possible. If a narcotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug, particularly when a sustained release formulation has been taken.

DOSAGE AND ADMINISTRATION

OxyContin[®] tablets should be swallowed whole and should not be broken, chewed, dissolved or crushed since this can lead to rapid release and absorption of a potentially fatal dose of oxycodone.

OxyContin 60 mg and 80 mg tablets, or a single dose greater than 40 mg, are for use in opioid tolerant patients only. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

OxyContin should not be used in the early post-operative period (12 - 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal. **OxyContin** is not indicated for rectal administration.

Adults: Individual dosing requirements vary considerably based on each patient's age, weight, severity and cause of pain, and medical and analgesic history.

Patients Not Receiving Opioids at the Time of Initiation of Oxycodone Treatment:

Oxy•IR[®] (oxycodone hydrochloride tablets)

The usual initial adult dose of **Oxy•IR** for patients who have not previously received opioid analgesics is 5 or 10 mg, po, every 6 hours.

OxyContin[®] (oxycodone hydrochloride controlled release tablets)

The usual initial adult dose of **OxyContin** for patients who have not previously received opioid analgesics is 10 or 20 mg every 12 hours.

Patients Currently Receiving Opioids: Patients currently receiving other oral oxycodone formulations may be transferred to **OxyContin** tablets at the same total daily oxycodone dosage, equally divided into two 12 hourly **OxyContin** doses.

For patients who are receiving an alternate opioid, the "oral oxycodone equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, TABLE 1 can be used to calculate the approximate daily oral oxycodone dosage that should provide equivalent analgesia. This total daily oral oxycodone dose should then be equally divided into two 12 hourly **OxyContin** doses. It is usually appropriate to treat a patient with only one opioid at a time.

Patients who are receiving 1 to 5 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine should be started on 10 to 20 mg **OxyContin** q12h. For patients receiving 6 to 9 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, a starting dose of 20 to 30 mg q12h should be used and for patients receiving 10 to 12 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, a starting dose of 30 to 40 mg q12h is suggested. For those receiving > 12 tablets/capsules per

day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, conversions should be based on the total daily opioid dose.

Use with Non-Opioid Medications: If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. **OxyContin** and **Oxy•IR** can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration: Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at regular administration of the lowest dose of controlled release oxycodone (OxyContin) which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response. In patients receiving **OxyContin**, the dose may be titrated at intervals of 24-36 hours to that which provides satisfactory pain relief without unmanageable side effects. **OxyContin** is designed to allow 12 hourly dosing.

If breakthrough pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration of controlled release oxycodone (OxyContin).

Adjustment or Reduction of Dosage: Following successful relief of pain, periodic attempts to re-assess the opioid analgesic requirements should be made. If treatment discontinuation is required, the dose of opioid may be decreased as follows: one-half of the previous daily dose given q12h (**OxyContin**) or q6h (**Oxy•IR**) for the first two days, followed thereafter by a 25% reduction every two days.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with these types of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

TABLE 1
OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES¹

Drug	Equivalent Dose (mg) ² (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10	60 ³	3-4
Oxycodone	15	30 ⁴	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine ⁶	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone ⁵	-	-	-
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4
Mixed Agonist-Antagonists⁷:			
Pentazocine ⁶	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

References:

¹ Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.

Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.

Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

² **Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25-50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.[†] Upward titration may be required to reach appropriate maintenance doses.**

[†]Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-1132.

³ **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2 - 3: 1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**

⁴ Based on single entity oral oxycodone in acute pain.

⁵ Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

⁶ Not recommended for the management of chronic pain.

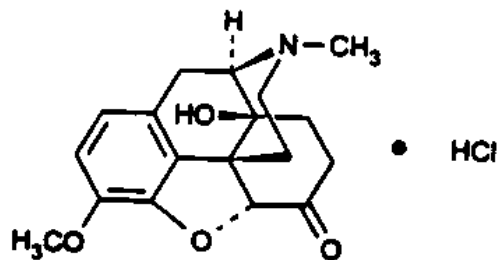
⁷ Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

PHARMACEUTICAL INFORMATION

Drug Substance: Oxycodone is a semi-synthetic derivative of the naturally occurring opium alkaloid, thebaine.

Proper Name: Oxycodone Hydrochloride

Structure:



Molecular Formula: C₁₈H₂₁NO₄•HCl

Chemical Name: 4,5αEpoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular Weight: 351.83

Appearance: White to off-white, odourless, crystalline powder.

Solubility: Soluble in water, slightly soluble in alcohol.

Melting Point: 218° to 223°C.

Composition:

Active Ingredient(s): Oxycodone Hydrochloride

Non-medicinal Ingredients:

OxyContin (all strengths): lactose, magnesium stearate, polymethyl acrylate, povidone, stearyl alcohol, talc and triacetin

5 mg Film Coating:

Opadry[®] Blue:

- FD&C Blue No.1
- hydroxypropyl methylcellulose
- polyethylene glycol
- titanium dioxide

15 mg Film Coating:

Opadry[®] Grey:

- hydroxypropyl methylcellulose
- iron oxide
- polyethylene glycol
- titanium dioxide

30 mg Film Coating:

Opadry[®] Brown:

- hydroxypropyl methylcellulose
- iron oxide
- polyethylene glycol
- polysorbate 80
- titanium dioxide

60 mg Film Coating:

Opadry[®] Red:

- hydroxypropyl methylcellulose
- iron oxide
- polyethylene glycol
- polysorbate 80
- titanium dioxide
- FD&C Red No. 40 Aluminum Lake

10 mg Film Coating:

Opadry[®] White:

- hydroxypropyl methylcellulose
- hydroxypropyl cellulose
- polyethylene glycol
- titanium dioxide

20 mg Film Coating:

Opadry[®] Pink:

- hydroxypropyl methylcellulose
- iron oxide
- polyethylene glycol
- polysorbate 80
- titanium dioxide

40 mg Film Coating:

Opadry[®] Yellow:

- hydroxypropyl methylcellulose
- iron oxide
- polyethylene glycol
- polysorbate 80
- titanium dioxide

80 mg Film Coating:

Opadry[®] Green:

- FD&C Blue No. 2 Aluminum Lake
- hydroxypropyl methylcellulose
- hydroxypropyl cellulose
- iron oxide
- polyethylene glycol
- titanium dioxide

Oxy•IR (all strengths): crospovidone, lactose, microcrystalline cellulose and stearic acid

Coating Suspension: Opadry[®] White:
- hydroxypropyl methylcellulose
- hydroxypropyl cellulose
- titanium dioxide
- polyethylene glycol

Stability and Storage Recommendations:

Store at room temperature (15°- 30°C). Keep in cool, dry place.

AVAILABILITY OF DOSAGE FORMS

OxyContin[®] (oxycodone hydrochloride controlled release tablets) 5 mg are round, unscored, pale blue, biconvex tablets imprinted with CDN on one side and the mg strength on the other. They are available in opaque plastic bottles of 50 tablets.

OxyContin[®] (oxycodone hydrochloride controlled release tablets) 10 mg are round, unscored, white, biconvex tablets imprinted with CDN on one side and the mg strength on the other. They are available in opaque plastic bottles of 50.

OxyContin[®] (oxycodone hydrochloride controlled release tablets) 15 mg are round, unscored, grey, biconvex tablets imprinted with CDN on one side and the mg strength on the other. They are available in opaque plastic bottles of 50 tablets.

OxyContin[®] (oxycodone hydrochloride controlled release tablets) 20 mg are round, unscored, pink, biconvex tablets imprinted with CDN on one side and the mg strength on the other. They are available in opaque plastic bottles of 50.

OxyContin[®] (oxycodone hydrochloride controlled release tablets) 30 mg are round, unscored, brown, biconvex tablets imprinted with CDN on one side and the mg strength on the other. They are available in opaque plastic bottles of 50 tablets.

OxyContin[®] (oxycodone hydrochloride controlled release tablets) 40 mg are round, unscored, yellow, biconvex tablets imprinted with CDN on one side and the mg strength on the other. They are available in opaque plastic bottles of 50 tablets.

OxyContin[®] (oxycodone hydrochloride controlled release tablets) 60 mg are round, unscored, red, biconvex tablets imprinted with CDN on one side and the mg strength on the other. They are available in opaque plastic bottles of 50 tablets.

OxyContin[®] (oxycodone hydrochloride controlled release tablets) 80 mg are round, unscored, green, biconvex tablets imprinted with CDN on one side and the mg strength on the other. They are available in opaque plastic bottles of 50 tablets.

Oxy•IR[®] (oxycodone hydrochloride tablets) 5 mg are round, scored, white, biconvex tablets imprinted with **Oxy•IR** on one side and 5 on the other. They are available in opaque plastic bottles of 50 tablets.

Oxy•IR[®] (oxycodone hydrochloride tablets) 10 mg are white, scored, capsule-shaped tablets imprinted with **Oxy•IR** on one side and 10 on the other. They are available in opaque plastic bottles of 50 tablets.

Oxy•IR[®] (oxycodone hydrochloride tablets) 20 mg are white, scored, oval shaped tablets imprinted with **Oxy•IR** on one side and 20 on the other. They are available in opaque plastic bottles of 50 tablets.

PHARMACOLOGY

Pharmacodynamics:

Oxycodone and related μ -agonist opioids produce their major effects on the CNS and the bowel by acting at specific saturable opioid receptors in the CNS and other tissues. The effects include analgesia, drowsiness, changes in mood, respiratory depression, cough suppression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous systems.

Oxycodone receptor selectivity has not been extensively studied or characterized, and there appears to be a discrepancy between its weak affinity for opioid receptors and its potent antinociceptive activity.

Oxycodone has been shown to be 2 - 4 times more potent than morphine after both subcutaneous and intraperitoneal administration in rats. In clinical studies in patients with acute post-operative pain, oxycodone has been demonstrated to be twice as potent as morphine.

TOXICOLOGY

The LD₅₀ after subcutaneous administration of oxycodone in mice was 275 - 340 mg/kg. The lowest lethal dose has been reported to be 200 mg/kg after subcutaneous administration in mice. These values are similar to those obtained for morphine. In a preliminary 12 day study in rabbits, no drug related toxic effects were discernable at 5 mg/kg. Doses of 25, 75 and 150 mg/kg were associated with variable and transient pharmacotoxic effects typical of high dose opioid treatment in animals (decreased activity, decreased or absent defecation and convulsions). Reproduction studies have been performed in rats and rabbits at doses up to 3 and 47 times, respectively, the usual human doses and have revealed no evidence of impaired fertility or harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women, and no studies on fertility or the post-natal effects of intrauterine exposure have been carried out.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5,000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1,500 µg/ml and with activation 48 hours after exposure at doses of up to 5,000 µg/ml, and in the in vivo bone marrow micronucleus test 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 1,250 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.

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PART III: CONSUMER INFORMATION^NOxyContin®

Oxycodone Hydrochloride Controlled Release Tablets

^NOxy-IR®

Oxycodone Hydrochloride Tablets

This leaflet is part III of a three-part "Product Monograph" published when OxyContin and Oxy-IR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OxyContin. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

OxyContin is an oral controlled release tablet that slowly releases oxycodone (an opioid analgesic) over a 12 hour period, and requires a dose every 12 hours to control your pain.

Oxy-IR is an oral immediate release tablet that releases oxycodone promptly, usually requiring a dose every 6 hours to control pain.

What it does:

Oxycodone is a medicine used to treat moderate to severe pain requiring the continuous use of an opioid analgesic preparation for several days or more.

Oxycodone belongs to a class of drugs which is commonly referred to as opiates, opioids or narcotics and also includes codeine, fentanyl, hydromorphone and morphine.

Your pain may increase or decrease occasionally and your doctor may need to change the amount of oxycodone you take daily (daily dosage).

When it should not be used:

OxyContin or **Oxy-IR** should not be used if:

- Your doctor did not prescribe it for you;
- You are allergic to oxycodone, opioids or any other ingredient in the tablets; (see **What the nonmedicinal ingredients are:**)
- Your pain is mild;
- Your pain can be controlled by occasional use of any painkillers;
- You have severe asthma or severe lung problems;
- You suffer from alcoholism;
- You have a head injury;
- You suffer from seizures;
- You had surgery less than 12-24 hours ago and you were not taking **OxyContin** just before surgery;
- You have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen;

- You are taking, or have taken within the past 2 weeks, a monoamine oxidase inhibitor medications (e.g., Nardil®, Parnate®);

Oxy-IR should be used with caution before surgery and within the first 12-24 hours after surgery.

Individuals under 18 years of age should not take **OxyContin** or **Oxy-IR** tablets.

Use of **OxyContin** or **Oxy-IR** tablets in pregnancy should be avoided to the extent possible. It is not clear what effects the medication would have on the fetus.

What the medicinal ingredient is:

Oxycodone Hydrochloride

What the nonmedicinal ingredients are:

OxyContin Controlled Release Tablets: hydroxypropyl methylcellulose (hypromellose), lactose, magnesium stearate, polyethylene glycol (Macrogol 400), polymethyl acrylate, povidone, stearyl alcohol, talc, titanium dioxide triacetin. In addition, the tablet coatings contain the following:
 5 mg – FD&C Blue No. 1 [brilliant blue]
 10 mg – hydroxypropylcellulose
 15 mg – iron oxide
 20 mg, 30 mg and 40 mg – polysorbate 80 and iron oxide
 60 mg – polysorbate 80 FD&C Red No. 40 Aluminum Lake and iron oxide
 80 mg – hydroxypropylcellulose, iron oxide and FD&C Blue No. 2 Aluminum Lake [indigo carmine].

Oxy-IR Immediate Release Tablets: crospovidone, lactose, microcrystalline cellulose, stearic acid. In addition, the tablet coating contains the following:
 hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol, titanium dioxide.

What dosage forms it comes in:

OxyContin Controlled Release Tablets: 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg.

Oxy-IR Immediate Release Tablets: 5 mg, 10 mg and 20 mg.

WARNINGS AND PRECAUTIONS

OxyContin tablets are designed to work properly over 12 hours when swallowed whole. If a tablet is broken, crushed, dissolved or chewed, the entire 12-hour dose will be absorbed rapidly into your body. This can be dangerous, causing serious problems such as an overdose, which can be fatal.

Keep OxyContin or Oxy-IR out of the reach of children. You should not give OxyContin or Oxy-IR to anyone as inappropriate use may have severe medical consequences, including death.

BEFORE you use **OxyContin** or **Oxy-IR**, talk to your doctor or pharmacist if you have, or had in the past any other medical conditions, especially the following ones: trouble breathing or lung problems, head injury, liver or kidney problems, adrenal gland problems, such as Addison's disease, convulsions or seizures, alcoholism, hallucinations or other severe mental problems, past or present substance abuse or drug addiction.

Tell your doctor or pharmacist if you are pregnant, plan to become pregnant, or are breastfeeding. **OxyContin** or **Oxy-IR** will pass through the milk and may harm the baby. **OxyContin** or **Oxy-IR** use should be avoided to the extent possible in patients who are pregnant or lactating. If your baby shows signs of more than usual increased sleepiness, difficulty breastfeeding, breathing difficulty, or limpness, talk to the baby's doctor immediately. If you cannot reach the doctor right away, take the baby to an emergency room.

If you are planning surgery, or about to undergo surgery, tell your doctor that you are taking **OxyContin**.

You should take the following precautions while taking **OxyContin** or **Oxy-IR** tablets:

- You must not consume alcohol while taking **OxyContin** or **Oxy-IR**, as it may increase the chance of experiencing dangerous side effects;
- Driving or other tasks requiring full alertness should not be attempted until you are sure that taking **OxyContin** or **Oxy-IR** does not make you drowsy;
- You must tell your doctor and pharmacist if you are taking any other over-the-counter or prescription medications - they will tell you what you should do.

Abuse, Addiction and Physical Dependence

There is a risk of abuse or addiction with all opioids. Some patients, particularly those who have abused drugs in the past, may have a higher risk of abusing or developing an addiction while taking opioids, such as **OxyContin** or **Oxy-IR**. Patients who have taken **OxyContin** or **Oxy-IR** for a period of time may develop physical dependence, and should not abruptly stop taking it. See '**Discontinuation:**' section of this leaflet.

While there are important differences between physical dependence and addiction, each is a reason for close medical supervision and honest discussions with your doctor. If you have questions or concerns about abuse, addiction or physical dependence, please tell your doctor.

INTERACTIONS WITH THIS MEDICATION

You should not take **OxyContin** or **Oxy-IR** if you are currently taking (or recently stopped taking) one of the medicines known as monoamine oxidase inhibitor medications (e.g., Nardil®, Parlate®).

Drugs that may interact with **OxyContin** or **Oxy-IR** include:

- Alcohol or other sedative drugs may enhance the drowsiness caused by oxycodone;
- Other opioids, anaesthetics, sedatives, hypnotics, antidepressants, sleeping aids, phenothiazines, neuroleptics, some heart medications (e.g., beta-blockers), chloral hydrate and glutethimide (not available in Canada);
- Antihistamines or sleep aids (these medicines could make you drowsy and depress your breathing);
- Any nonprescription, (over-the-counter) medications;
- Any herbal remedies.

PROPER USE OF THIS MEDICATION

OxyContin tablets must be swallowed whole and should not be broken, chewed, dissolved or crushed since this can lead to the release and absorption of an excessive dose of oxycodone which can seriously harm you.

OxyContin is not recommended for rectal administration.

Usual dose:

Take the dose prescribed by your doctor. **OxyContin** tablets should be taken every 12 hours (with 4 to 6 oz. of water) to prevent pain all day and night.

Oxy-IR tablets should be taken, usually every 6 hours (with 4 to 6 oz. of water), as directed by your doctor.

Your dose of OxyContin or Oxy-IR will be clearly labelled on the medication bottle. Be sure to follow the directions on the label exactly; this is very important. Do not increase or decrease your dose without consulting your doctor. If your dosage is changed by your doctor, be sure to write it down at the time your doctor calls or sees you, and follow the new directions exactly. Review your pain regularly with your doctor to determine if you still need **OxyContin** or **Oxy-IR**. Be sure to use **OxyContin** or **Oxy-IR** only for the condition for which it was prescribed.

You may see tablets in your stools (bowel movements) when using **OxyContin**. Do not be concerned, your body has absorbed the medicine.

Discontinuation:

After you stop taking **OxyContin** or **Oxy-IR** you should take the unused tablets to your pharmacist to be destroyed.

Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms such as body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, unexplained fever, weakness and yawning.

You should not stop taking **OxyContin** or **Oxy-IR** all at once if you have been taking it for more than a few days.

Reordering OxyContin/Oxy-IR:

A new written prescription is required from your doctor each time you need more **OxyContin** or **Oxy-IR**. Therefore, it is important that you contact your doctor at least three working days before your current supply runs out.

Overdose:

The most important sign of overdose is decreased breathing (abnormally slow or weak breathing), dizziness, confusion or extreme drowsiness. If you accidentally take an overdose of **OxyContin** or **Oxy-IR**, call your doctor and/or your local emergency number and/or a Regional Poison Control Centre immediately, or go to a hospital emergency and take any remaining tablets and the container with you, even though you may not feel sick.

Missed Dose:

It is very important that you do not miss any doses. If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once, unless your doctor tells you to. If you miss several doses in succession, talk to your doctor before restarting your medication.

Do not seek additional prescriptions for this medicine from any other doctor - unless responsibility for your pain management has been transferred to another doctor.

Should your pain increase, or any other complaint develop as a result of taking **OxyContin** or **Oxy-IR** tell your doctor immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects you may experience are constipation, nausea, drowsiness, dizziness, vomiting, itching, headache, dry mouth, weakness and sweating. Tell your doctor about these problems if they arise. Your doctor may order a laxative and stool softener to help relieve your constipation while you are taking **OxyContin** or **Oxy-IR**.

If you experience any symptoms related to difficulty in breathing, such as tight chest or wheezing, fainting, or rapid heartbeat, please consult a doctor or pharmacist immediately.

Physical dependence, abuse and withdrawal reactions have been rarely reported. See withdrawal reactions listed within the **‘Discontinuation:’** section of this leaflet.

*This is not a complete list of side effects. For any unexpected effects while taking **OxyContin** or **Oxy-IR**, contact your doctor or pharmacist.*

HOW TO STORE IT

Store at room temperature (15-30°C). Keep in a cool, dry place.

Keep **OxyContin** or **Oxy-IR** in a secure place to prevent theft and misuse.

Do not give **OxyContin** or **Oxy-IR** to anyone other than the person for whom it was prescribed, since it may seriously harm them, including death

Keep **OxyContin** or **Oxy-IR** out of the reach of children. Accidental overdose by a child is dangerous and may result in death.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
 By toll-free fax: 866-678-6789
 Online: www.healthcanada.gc.ca/medeffect
 By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
 Canada Vigilance National Office
 Marketed Health Products Safety and
 Effectiveness Information Bureau
 Marketed Health Products Directorate
 Health Products and Food Branch
 Health Canada
 Tunney’s Pasture, AL 0701C
 Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

*This leaflet summarized important information about **OxyContin** or **Oxy-IR**. If you would like more information, talk with your doctor and/or pharmacist.*

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.purdue.ca/products>
 or by contacting the manufacturer, Purdue Pharma, at:
 1-800-387-5349.

This leaflet was prepared by Purdue Pharma.

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