PRODUCT MONOGRAPH

[N]Sandoz Oxycodone CR

Oxycodone Hydrochloride Controlled Release Tablets
5 mg

Oxycodone Hydrochloride Controlled Release Tablets, Manufacturer's Standard
10 mg, 20 mg, 40 mg, 80 mg

Opioid Analgesic

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Controlled Release Tablet / 5, 10, 20, 40, 80 mg	microcrystalline cellulose, copovidone, behenoyl polyoxylglycerides, hypromellose, lactose monohydrate, magnesium stearate, maize starch, colloidal anhydrous silica , stearic acid, triglycerides, titanium dioxide, hydrogenated castor oil. Colouring agents excipients in the coating: 5 mg Film-Coating: Indigo carmine, hydrated aluminum oxide, quinoline yellow; 10 mg Film-Coating: None: 20 mg Film-Coating: red iron: 40 mg Film-Coating: yellow iron oxide: 80 mg Film-Coating: hydrated aluminum oxide, indigo carmine, black iron oxide, quinoline yellow 80 (mg).

INDICATIONS AND CLINICAL USE

Sandoz Oxycodone CR (oxycodone hydrochloride) controlled release tablets are indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment and:

- that is opioid-responsive; and
- for which alternative options are inadequate

Sandoz Oxycodone CR is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age):
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac

function, concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

Pediatrics (< 18 years of age):
The safety and efficacy of Sandoz Oxycodone CR has not been studied in the pediatric population. Therefore the use of Sandoz Oxycodone CR is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

Sandoz Oxycodone CR (oxycodone hydrochloride) controlled release tablets are contraindicated for:

- Patients who are hypersensitive to the active substance (oxycodone) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain.
- Patients with acute asthma or other obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Limitations of Use**
  Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with controlled release opioid formulations, Sandoz Oxycodone CR should only be used in patients for whom alternative treatment options (eg. non-opioid analgesic) are ineffective, not tolerated or would be otherwise inadequate to provide appropriate management of pain (e.g., immediate-release opioids) (see DOSAGE AND ADMINISTRATION).

- **Addiction, Abuse, and Misuse**
  Sandoz Oxycodone CR poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Sandoz Oxycodone CR and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Sandoz Oxycodone CR should be stored securely to avoid theft or misuse.

- **Life-threatening Respiratory Depression**
  Serious, life-threatening, or fatal respiratory depression may occur with use of Sandoz Oxycodone CR. Patients should be monitored for respiratory depression, especially during initiation of Sandoz Oxycodone CR or following a dose increase. Sandoz Oxycodone CR should be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Sandoz Oxycodone CR tablets can lead to rapid release and absorption of a potentially fatal dose of oxycodone (see WARNINGS AND PRECAUTIONS).

- **Accidental Exposure**
  Accidental consumption of even one dose of Sandoz Oxycodone CR especially by children, can result in a fatal overdose of oxycodone (see DOSAGE AND ADMINISTRATION subsection Disposal, for instructions on proper disposal).

- **Neonatal Opioid Withdrawal Syndrome**
  Prolonged maternal use of Sandoz Oxycodone CR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

General

Sandoz Oxycodone CR 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 of oxycodone, or total daily doses greater than 80 mg of oxycodone, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids (see WARNINGS AND PRECAUTIONS, Drug Interactions).

Patients should be instructed not to give Sandoz Oxycodone CR 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 Sandoz Oxycodone CR, as it may increase the chance of experiencing dangerous side effects.

Hyperalgesia that will not respond to a further dose increase of oxycodone, may occur at particularly high doses. An oxycodone dose reduction or change in opioid may be required.

Addiction, Abuse and Misuse

Like all opioid, Sandoz Oxycodone CR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Sandoz Oxycodone CR should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Sandoz Oxycodone CR should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain

Carcinogenesis and Mutagenesis

See **TOXICOLOGY** section.

Cardiovascular

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.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Sandoz Oxycodone CR and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opiate receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist.

Use in Drug and Alcohol Addiction

Sandoz Oxycodone CR is an opioid 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.

Gastrointestinal Effects

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.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioid during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of Sandoz Oxycodone CR is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic

Interactions with Central Nervous System Depressants (Including Alcohol):

Sandoz Oxycodone CR should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. Sandoz Oxycodone CR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

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

Peri-Operative Considerations:

Sandoz Oxycodone CR is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Sandoz Oxycodone CR for at least 24 hours before the operation and Sandoz Oxycodone CR should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Sandoz Oxycodone CR is to be continued after the patient recovers from the postoperative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

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.

Sandoz Oxycodone CR 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.

Psychomotor Impairment

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.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Sandoz Oxycodone CR, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Sandoz Oxycodone CR and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of Sandoz Oxycodone CR are essential (see DOSAGE AND ADMINISTRATION). Overestimating the Sandoz Oxycodone CR dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Patient Counselling Information:

A patient information sheet should be provided when Sandoz Oxycodone CR tablets are dispensed to the patient.

Patients receiving Sandoz Oxycodone CR should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal consequences.

2. Patients should be advised that Sandoz Oxycodone CR contains oxycodone, an opioid pain medicine.

3. Patients should be advised that Sandoz Oxycodone CR should only be taken as directed. The dose of Sandoz Oxycodone CR should not be adjusted without consulting with a physician.

4. Sandoz Oxycodone CR must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal oxycodone overdose.

5. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

6. Patients should not combine Sandoz Oxycodone CR with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.

7. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with Sandoz Oxycodone CR.

8. Patients should be advised that if they have been receiving treatment with Sandoz Oxycodone CR and cessation of therapy is indicated, it may be appropriate to taper Sandoz Oxycodone CR dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms (see ADVERSE REACTIONS, Withdrawal (Abstinence) Syndrome).

9. Patients should be advised that the most common adverse reactions that may occur while taking Sandoz Oxycodone CR are asthenic conditions, constipation, dizziness, dry mouth, headache, nausea, pruritus, somnolence, sweating and vomiting.

10. 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.

11. Patients should be advised that Sandoz Oxycodone CR may cause drowsiness, dizziness or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients

started on Sandoz Oxycodone CR or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of Sandoz Oxycodone CR.

12. Patients should be advised that Sandoz Oxycodone CR is a potential drug of abuse. They should protect it from theft or misuse.

13. Patients should be advised that Sandoz Oxycodone CR should never be given to anyone other than the individual for whom it was prescribed.

14. Patients should be advised that Sandoz Oxycodone CR 80 mg tablets or a single dose greater than 40 mg are for use only in individuals tolerant to the effect of opioids.

15. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with Sandoz Oxycodone CR. Women who are breastfeeding or pregnant should not use Sandoz Oxycodone CR.

Special Populations

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

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 oxycodone hydrochloride; by 50 - 60% in patients with moderate degrees of renal impairment; and by approximately two-fold in patients with hepatic cirrhosis.

Pregnant Women: Animal reproduction studies have revealed no evidence of harm to the fetus due to oxycodone, however, as studies in humans have not been conducted, Sandoz Oxycodone CR is contraindicated in patients who are pregnant (see CONTRAINDICATIONS).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see WARNINGS AND PRECAUTIONS – NEONATAL OPIOID WITHDRAWAL SYNDROME).

Labour, Delivery and Nursing Women: In view of the potential for opioids to cross the placental barrier and to be excreted in breast milk, Sandoz Oxycodone CR is contraindicated during labour or in nursing mothers. Physical dependence or respiratory depression may occur in the infant if opioids are administered during labour.

Pediatrics (< 18 years of age): The safety and efficacy of Sandoz Oxycodone CR have not been studied in the pediatric population. Therefore, use of Sandoz Oxycodone CR is not recommended in patients under 18 years of age.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION**).

"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 oxycodone hydrochloride tablets.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of oxycodone hydrochloride controlled release 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 oxycodone hydrochloride 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, tumour 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. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with opioid analgesics and include those reported in oxycodone hydrochloride 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, edema peripheral, 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, cholestatis, dental caries, 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, 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.

DRUG INTERACTIONS

Overview

Interactions with Central Nervous System (CNS) Depressants: 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 taking other central nervous system depressants (eg. other opioids, sedatives, hypnotics, anti-depressants, phenothiazines, neuroleptics, antihistamines and anti-emetics) and beta-blockersas they may enhance the CNS-depressant effect (eg. respiratory depression) of Sandoz Oxycodone CR. Sandoz Oxycodone CR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Drugs Metabolized by Cytochrome P450 Isozymes: Oxycodone is metabolized in part by cytochrome CYP 2D6 and cytochrome P450 3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various coadministered drugs or dietary elements, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly.

Inhibitors of CYP3A4:
Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone hydrochloride, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin, clarithromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and Cmax by 3.6 and 1.7 fold, respectively. Although clinical studies have not been conducted with other CYP3A4 inhibitors, the expected clinical results would be increased or prolonged opioid effects. If co-administration with Sandoz Oxycodone CR is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP450 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inducers of CYP3A4:
CYP450 inducers, such as rifampin, carbamazepine and phenytoin, and St. John's wort, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, the development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63%

respectively. If coadministration with Sandoz Oxycodone CR is necessary, caution is advised when initiating therapy with, currently taking or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inhibitors of CYP2D6:
Oxycodone is metabolized in part to oxymorphone via cytochrome CYP2D6. 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 been shown to be of clinical significance during oxycodone treatment.

Administration with Mixed Activity Agonist/Antagonist Opioids
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.

MAO Inhibitors
MAO Inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. Sandoz Oxycodone CR is contraindicated in patients receiving MAO Inhibitors or who have used them within the previous 14 days (see CONTRAINDICATIONS).

Warfarin and Other Coumarin Anticoagulants: Clinically relevant changes in International Normalized Ratio (INR or Quick-value) in both directions have been observed in individuals when oxycodone and coumarin anticoagulants are co-administered.

Drug-Food Interactions
Administration of oxycodone hydrochloride controlled release tablets with food results in an increase in peak plasma oxycodone concentration of up to 1.5-fold but has no significant effect on the extent of absorption of oxycodone.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, General).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Sandoz Oxycodone CR should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.

Sandoz Oxycodone CR must **be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Sandoz Oxycodone CR tablets can lead to rapid release and absorption of a potentially fatal dose of oxycodone (see WARNINGS AND PRECAUTIONS).**

Sandoz Oxycodone CR 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.

Sandoz Oxycodone CR 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.

Sandoz Oxycodone CR is not indicated for rectal administration. The controlled release tablets may be taken with or without food, with a glass of water.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy. The dosage should be adjusted to the lowest Sandoz Oxycodone CR dose that will achieve the goal of satisfactory pain relief with acceptable side effects.

Recommended Dose and Dosage Adjustment

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: The usual initial adult dose of Sandoz Oxycodone CR 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 Sandoz Oxycodone CR tablets at the same total daily oxycodone dosage, equally divided into two 12 hourly Sandoz Oxycodone CR 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 Sandoz Oxycodone CR doses. It is usually appropriate to treat a patient with only one opioid at a time. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

Table 1: Opioid Analgesics: Approximate Analgesic Equivalences[1]

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-Antagonists[7]			
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.

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 Sandoz Oxycodone CR 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. Sandoz Oxycodone CR 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 the regular administration of the lowest dose of controlled release oxycodone (Sandoz Oxycodone CR) 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 Sandoz Oxycodone CR, the dose may be titrated at intervals of 24-36 hours to that which provides satisfactory pain relief without unmanageable side effects. Sandoz Oxycodone CR is designed to allow 12 hourly dosing.

If 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 (Sandoz Oxycodone CR**).**

Adjustment or Reduction of Dosage: Following successful relief of pain, periodic attempts to reassess 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 Sandoz Oxycodone CR for the first two days, followed thereafter by a 25% reduction every two days.

Withdrawal symptoms may occur following abrupt discontinuation of therapy. These symptoms may include 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.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild.

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.

Missed Dose
If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

Disposal
Sandoz Oxycodone CR should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. Sandoz Oxycodone CR should not be used in front of children, since they may copy these actions.

Unused or expired Sandoz Oxycodone CR should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. Sandoz Oxycodone CR should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

Sandoz Oxycodone CR should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

OVERDOSAGE

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

Symptoms: Serious overdosage 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, miosis, hypotonia, cold and clammy skin, and sometimes bradycardia and hypotension. Severe overdosage 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 CO_2, 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.

Pharmacodynamics

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.

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.

Studies with oxycodone hydrochloride controlled release tablets and oxycodone hydrochloride immediate release 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 oxycodone hydrochloride controlled release tablets (20 and 30 mg) was greater than that of 10 mg oxycodone hydrochloride controlled release tablets 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, oxycodone hydrochloride controlled release tablets q12h was more effective than placebo in decreasing pain and in improving quality of life, mood and sleep. In patients with cancer pain, oxycodone hydrochloride controlled release tablets administered q12h produced equivalent analgesia to immediate release oxycodone hydrochloride tablets administered four times per day. In patients with low back pain, oxycodone hydrochloride controlled release tablets q12h and immediate release oxycodone hydrochloride given four times per day, were equally effective. Titration to

analgesic effect was achieved as easily with oxycodone hydrochloride controlled release tablets as with immediate release oxycodone hydrochloride tablets.

Central Nervous System: Oxycodone produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough centre 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 oxycodone overdose.

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 the 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.

Endocrine System: Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifested from these hormonal changes.

Immune System: In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

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 papillary constriction, sedation, overall subjective "drug effect", analgesia and feelings of "relaxation".

The minimum effective analgesic concentration 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 Reaction Relationship

There is a significant relationship between increasing oxycodone plasma concentrations and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related side effects.

The dose of Sandoz Oxycodone CR 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

The activity of Sandoz Oxycodone CR is primarily due to the parent drug oxycodone. Sandoz Oxycodone CR is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving Sandoz Oxycodone CR impairs the controlled release delivery mechanism and could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. The high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Distribution

Following intravenous administration, the steady-state volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37ºC 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.

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs (see DRUG INTERACTIONS).

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and is present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent.

Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and β-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration in to the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion
Oxycodone and its metabolites are excreted in both urine and feces. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Pharmacokinetic studies of oxycodone hydrochloride controlled release tablets 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, oxycodone hydrochloride controlled release tablet 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.

In steady state pharmacokinetic studies of oxycodone hydrochloride controlled release tablets 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 oxycodone hydrochloride controlled release tablets. Steady-state was achieved within 24-36 hours of initiation of dosing. The absorption of oxycodone from oxycodone hydrochloride controlled release tablets is not significantly influenced when administered in the presence of food.

Special Populations and Conditions
Pediatrics: oxycodone hydrochloride controlled release tablets has not been studied in children and is not indicated for patients less than 18 years of age.

Geriatrics: Plasma concentrations of oxycodone are increased by approximately 15% in elderly subjects receiving oxycodone hydrochloride controlled release tablets.

Race: No data available.

Hepatic Insufficiency: Plasma concentrations of oxycodone are increased by approximately 2-fold in patients with hepatic cirrhosis.

Renal Insufficiency: Plasma concentrations of oxycodone are increased by 50% to 60% in patients with moderate degrees of renal impairment.

Genetic Polymorphism: No data available.

STORAGE AND STABILITY

Store between 15° and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Oxycodone CR (oxycodone hydrochloride controlled-release tablets) 5 mg are round, biconvex, turquoise tablet with embossment "SZ" on one side and "5" on the other side. They are available in opaque plastic bottles of 20, 50, and 100 tablets.

Sandoz Oxycodone CR (oxycodone hydrochloride controlled-release tablets) 10 mg are round, biconvex, white tablets without embossment. They are available in opaque plastic bottles of 20, 50, and 100 tablets.

Sandoz Oxycodone CR (oxycodone hydrochloride controlled-release tablets) 20 mg are round, biconvex, pink tablets without embossment. They are available in opaque plastic bottles of 20, 50, and 100 tablets.

Sandoz Oxycodone CR (oxycodone hydrochloride controlled-release tablets) 40 mg are round, biconvex, yellow tablets without embossment. They are available in opaque plastic bottles of 20, 50, and 100 tablets.

Sandoz Oxycodone CR (oxycodone hydrochloride controlled-release tablets) 80 mg are round, biconvex, green tablets without embossment. They are available in opaque plastic bottles of 20, 50, and 100 tablets.

Composition:
Active Ingredient(s): Oxycodone Hydrochloride

Nonmedicinal Ingredients:
Sandoz Oxycodone CR (all strengths): microcrystalline cellulose, copovidone, behenoyl polyoxylglycerides, hypromellose, lactose monohydrate, magnesium stearate, maize starch, colloidal anhydrous silica, stearic acid, triglycerides, titanium dioxide, hydrogenated castor oil.
Colouring agents excipients in the coating:
5 mg Film-Coating: Indigo carmine, hydrated aluminum oxide, quinoline yellow
10 mg Film-Coating: None
20 mg Film-Coating: Red iron oxide
40 mg Film-Coating: Yellow iron oxide
80 mg Film-Coating: Hydrated aluminum oxide, indigo carmine, black iron oxide, quinoline yellow

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

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

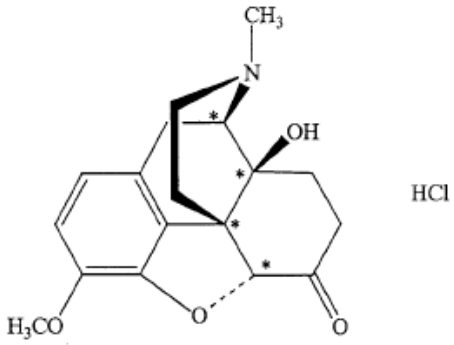
Proper name: Oxycodone Hydrochloride

Chemical name: 4,5 α epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular formula: $C_{18}H_{21}NO_4$•HCl

Molecular mass: 351.9 g/mol

Structural formula:



*Chiral Centres

Physicochemical properties: Oxycodone hydrochloride is a white to off-white, odourless, crystalline powder. It is soluble in water and slightly soluble in alcohol and has a melting point of 270°C to 275°C.

CLINICAL TRIALS

Comparative Bioavailability Studies

5 mg Tablet:

Blinded, Randomized, Single-Dose, 2-Way Crossover, Comparative Bioavailability Study to Compare Sandoz Oxycodone CR (oxycodone hydrochloride) 5 mg Controlled-Release Tablets versus OxyContin® (oxycodone hydrochloride) 5 mg Controlled-Release Tablets in 24 Healthy Male Subjects (18-55 years old) under Fasting Conditions.

Summary table of the comparative bioavailability data

Oxycodone (1 x 5 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test *	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng·h/mL)	57.020 59.305 (28)	58.330 60.837 (29)	97.75	91.87 to 104.01
AUC_{0-inf} (ng·h/mL)	58.214 60.436 (28)	60.024 62.551 (29)	96.98	91.39 to 102.92
C_{max} (ng/mL)	5.806 5.977 (23)	4.897 5.051 (24)	118.56	112.58 to 124.87
T_{max} § (h)	2.52 (40)	2.47 (42)		
$T_{½ el}$ § (h)	4.34 (12)	5.06 (12)		

* Sandoz Oxycodone CR 5 mg tablet manufactured for Sandoz Canada.

† OxyContin® 5 mg Controlled-Release Tablets (Purdue Pharma, Canada.)

§ Expressed as the arithmetic mean (CV%) only.

10 mg Tablet:

Blinded, Randomized, Single-Dose, 3-Way Crossover, Comparative Bioavailability Study to Compare Sandoz Oxycodone CR (oxycodone hydrochloride) 10 mg Controlled-Release Tablets versus OxyContin® (oxycodone hydrochloride) 10 mg Controlled-Release Tablets in 22 Healthy

Male Subjects (21-42 years old) under Fasting Conditions.

Summary table of the comparative bioavailability data

Oxycodone (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test *	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (pg·h/mL)	133739.68 138225.79 (23.95)	125924.10 129037.07 (21.02)	106.21	101.40 to 111.24
AUC_{0-inf} (pg·h/mL)	136770.17 141254.87 (23.66)	132193.88 135203.70 (19.87)	103.46	98.96 to 108.16
C_{max} (pg/mL)	11303.99 11492.12 (16.76)	10385.99 10502.17 (14.86)	108.84	102.63 to 115.43
T_{max} § (h)	3.00 (63.68)	1.84 (56.75)		
$T_{½\ el}$ § (h)	4.75 (14.23)	7.05 (17.01)		

* Sandoz Oxycodone CR 10 mg tablet manufactured for Sandoz Canada.
† OxyContin® 10 mg Controlled-Release Tablets (Purdue Pharma, Canada.)
§ Expressed as the arithmetic mean (CV%) only.

Blinded, Randomized, Multiple-Dose, 3-Way Crossover, Comparative Bioavailability Study to Compare Sandoz Oxycodone CR (oxycodone hydrochloride) 10 mg Controlled-Release Tablets versus OxyContin® (oxycodone hydrochloride) 10 mg Controlled-Release Tablets in 22 Healthy Male Subjects (21-42 years old) under Fasting Conditions.

Summary table of the comparative bioavailability data

Oxycodone (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{tau} (pg·h/mL)	132001.32 136766.76 (21.56)	132676.19 137366.61 (23.43)	99.49	95.73 to 103.40
C_{max} (pg/mL)	15705.56 16114.04 (17.88)	15823.64 16186.08 (18.26)	99.25	95.32% to 103.35
C_{min} (pg/mL)	5709.96 6145.13 (34.27)	6072.22 6552.66 (35.10)	94.03	86.94 to 101.71
T_{max}§ (h)	2.08 (48.74)	2.17 (58.42)		
FL§ (%)	90.33 (25.91)	87.76 (24.82)		

* Sandoz Oxycodone CR 10 mg tablet manufactured for Sandoz Canada.
† OxyContin®10 mg Controlled-Release Tablets (Purdue Pharma, Canada).
§ Expressed as the arithmetic mean (CV%) only.

Blinded, Randomized, Single-Dose, Blinded, 3-Way Crossover, Comparative Bioavailability Study to Compare Sandoz Oxycodone CR (oxycodone hydrochloride) 10 mg Controlled-Release Tablets versus OxyContin® (oxycodone hydrochloride) 10 mg Controlled-Release Tablets in 24 Healthy Male Subjects (23-43 years old) under Fed Conditions.

Summary table of the comparative bioavailability data

Oxycodone (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (pg·h/mL)	116890.29 119956.83 (24.98)	111590.46 113842.49 (20.02)	104.75	100.87 to 108.77
AUC_{0-inf} (pg·h/mL)	119192.82 122259.89 (24.76)	116930.71 119167.92 (19.51)	101.93	98.38 to 105.62
C_{max} (pg/mL)	12216.08 12483.17 (21.53)	10611.13 10896.86 (23.95)	115.13	108.97 to 121.62
T_{max}§ (h)	2.22 (40.39)	2.71 (51.33)		
$T_{½\ el}$§ (h)	4.30 (11.10)	6.40 (12.59)		

* Sandoz Oxycodone CR 10 mg tablet manufactured for Sandoz Canada.
† OxyContin® 10 mg Controlled-Release Tablets (Purdue Pharma, Canada).
§ Expressed as the arithmetic mean (CV%) only.

40 mg Tablet:
Blinded, Randomized, Single-Dose, 3-Way Crossover, Comparative Bioavailability Study to Compare Sandoz Oxycodone CR (oxycodone hydrochloride) 40 mg Controlled-Release Tablets versus OxyContin® (oxycodone hydrochloride) 40 mg Controlled-Release Tablets in 15 Healthy Adult Male Volunteers (18-44 years old) under Fasting Conditions.

Summary table of the comparative bioavailability data

Oxycodone (1 x 40 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng*h/mL)	531.85 568.36 (36)	504.29 531.06 (27)	105.47	99.23 – 112.10
AUC_I (ng*h/mL)	535.95 572.94 (36)	514.19 542.05 (27)	104.23	97.87 – 111.00
C_{max} (ng/mL)	47.40 50.07 (35)	42.84 44.86 (28)	110.63	103.71 - 118.01
T_{max}§ (h)	2.84 (36)	2.32 (34)		
$T_{½}$§ (h)	4.84 (7)	5.42 (20)		

* Sandoz Oxycodone CR 40 mg tablet manufactured for Sandoz Canada.
† OxyContin® 40 mg Controlled-Release Tablets (Purdue Pharma, Canada).
§ Expressed as the arithmetic mean (CV%) only.

Blinded, Randomized, Multiple-Dose, 3-Way Crossover, Comparative Bioavailability Study to Compare Sandoz Oxycodone CR (oxycodone hydrochloride) 40 mg Controlled-Release Tablets versus OxyContin® (oxycodone hydrochloride) 40 mg Controlled-Release Tablets in 15 Healthy Adult Male Volunteers (18-44 years old) under Fasting Conditions.

Summary table of the comparative bioavailability data

Oxycodone (1 x 40 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{tau} (ng*h/mL)	478.61 496.52 (24)	495.77 519.42 (27)	96.54	92.55 – 100.70
C_{max} (ng/mL)	58.74 60.52 (20)	59.20 61.36 (22)	99.22	
C_{min} (ng/mL)	18.02 19.10 (30)	20.97 22.44 (32)	85.94	
T_{max}§ (h)	2.31 (37)	2.23 (44)		
FL§ (%)	102.19 (13)	92.62 (18)		

* Sandoz Oxycodone CR 40 mg tablet manufactured for Sandoz Canada.
† OxyContin® 40 mg Controlled-Release Tablets (Purdue Pharma, Canada).
§ Expressed as the arithmetic mean (CV%) only.

Blinded, Randomized, Single-Dose, 2-Way Crossover, Comparative Bioavailability Study to Compare Sandoz Oxycodone CR (oxycodone hydrochloride) 40 mg Controlled-Release Tablets versus OxyContin® (oxycodone hydrochloride) 40 mg Controlled-Release Tablets in 13 Healthy Adult Male Volunteers (21-44 years old) under Fed Conditions.:

Summary table of the comparative bioavailability data

Oxycodone (1 x 40 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng*h/mL)	571.71 593.89 (28)	534.64 552.73 (29)	106.93	103.04 - 110.98
AUC_I (ng*h/mL)	574.74 597.26 (28)	542.49 561.26 (29)	105.94	101.95 - 110.10
C_{max} (ng/mL)	58.13 60.39 (27)	51.65 52.26 (17)	112.53	105.81 - 119.67
T_{max}§ (h)	3.27 (41)	2.97 (46)		
$T_{½}$§ (h)	4.32 (9)	5.72 (11)		

* Sandoz Oxycodone CR 40 mg manufactured for Sandoz Canada.
† OxyContin® 40 mg Controlled-Release Tablets (Purdue Pharma, Canada).
§ Expressed as the arithmetic mean (CV%) only.

DETAILED 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 LD_{50} 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).

Teratogenicity:
Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a study of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses ≥2 mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day). There were no effects on the F2 generation at any dose in the study.

There are 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.

Mutagenicity:
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 mcg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 mcg/ml and with activation 48 hours after exposure at doses of up to 5000 mcg/ml, and in the in vivo bone marrow micronucleus test in mice at plasma levels of up to 48 mcg/ml. Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 mcg/ml) at 24 but not 48 hours of exposure and in the mouse

lymphoma assay at doses of 50 mcg/ml or greater with metabolic activation and at 400 mcg/ml or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Carcinogenicity:
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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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Sandoz Oxycodone CR
Oxycodone Hydrochloride Controlled Release Tablets
5 mg
Oxycodone Hydrochloride Controlled Release Tablets, Manufacturer's Standard
10 mg, 20 mg, 40 mg, 80 mg

Read this carefully before you start taking Sandoz Oxycodone CR and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Sandoz Oxycodone CR.

Serious Warnings and Precautions

- **Even if you take Sandoz Oxycodone CR as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse, you should speak to your prescriber (eg. doctor).**
- **Life-threatening breathing problems can happen while taking Sandoz Oxycodone CR, especially if not taken as directed.**
- **Never give anyone your Sandoz Oxycodone CR. They could die from taking it. If a person has not been prescribed Sandoz Oxycodone CR, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **Babies born to mothers who have taken Sandoz Oxycodone CR (for short or long periods, in small or large doses) during their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness), or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.**

What is Sandoz Oxycodone CR used for?

Sandoz Oxycodone CR is used for the long-term management of pain, when:
- the pain is severe enough to require daily, around-the-clock pain medication
- the doctor determines that other treatment options are not able to effectively manage your pain

Sandoz Oxycodone CR is NOT used ("as needed") to treat pain that you only have once in a while.

How does Sandoz Oxycodone CR work?

Sandoz Oxycodone CR contains oxycodone which is a pain medication belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in Sandoz Oxycodone CR?
Medicinal ingredients: Oxycodone Hydrochloride

Non-medicinal ingredients: Sandoz Oxycodone CR Tablets: microcrystalline cellulose, copovidone, behenoyl polyoxylglycerides, hypromellose, lactose monohydrate, magnesium stearate, maize starch, colloidal anhydrous silica, stearic acid, triglycerides, titanium dioxide, hydrogenated castor oil.

In addition, the tablet coatings contain the following colouring agents:
5 mg: Indigo carmine, hydrated aluminum oxide, quinoline yellow
10 mg – none
20 mg – red iron oxide
40 mg – yellow iron oxide
80 mg – hydrated aluminium oxide, indigo carmine, black iron oxide, quinolone yellow

Sandoz Oxycodone CR comes in the following dosage forms:
Sandoz Oxycodone CR Tablets: 5 mg, 10 mg, 20 mg, 40 mg, 80 mg.

Do not use Sandoz Oxycodone CR if:

- you are allergic to oxycodone hydrochloride, other opioids, or any of the other ingredients of Sandoz Oxycodone CR
- your pain can be controlled by the occasional use of pain medications including those available without a prescription
- you have severe asthma, trouble breathing, or any heart problems
- you have bowel blockage or narrowing of the stomach or intestines (eg. paralytic ileus)
- you have severe pain in your abdomen
- you have a head injury or other risks for seizures
- you suffer from alcoholism
- you have an irregular heartbeat
- you are pregnant or plan to become pregnant, breastfeeding, or in labour
- you are under 18 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Oxycodone CR. Talk about any health conditions or problems you

may have, including if you:

- have severe kidney, liver disease
- are going to have or recently had, a planned surgery
- Have a history of illicit or prescription drug or alcohol abuse
- have past or current depression
- have problems with your thyroid, adrenal or prostate gland
- suffer from chronic or severe constipation

have, or had in the past hallucinations or other severe mental problems

Other warnings you should know about:

There are important differences between physical dependence and addiction, and 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.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to Sandoz Oxycodone CR. Drowsiness, dizziness, or light-headedness, can especially occur after the first dose and when the dose is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Sandoz Oxycodone CR:

- alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking Sandoz Oxycodone CR. This can lead to drowsiness, depressed breathing, serious side effects or a fatal overdose.
- other sedative drugs which may enhance the drowsiness caused by Sandoz Oxycodone CR
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). Do not take Sandoz Oxycodone CR with monoamine oxide (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with Sandoz Oxycodone CR.
- drugs used to treat serious mental or emotional disorders such as schizophrenia
- antihistamines (for allergies)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
- some heart medications (beta blockers)
- anti-retroviral, azole anti-fungal and macrolide antibiotic drugs

How to take Sandoz Oxycodone CR:

Swallow whole. Do not break, chew, dissolve or crush the tablet as this leads to quick release and absorption of a higher dose of oxycodone over a short period of time that may cause death.

Usual dose:
Take the dose prescribed by your doctor. Sandoz Oxycodone CR tablets should be taken every 12 hours with a glass of water.

Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly.

Your dose of Sandoz Oxycodone CR 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 Sandoz Oxycodone CR. Be sure to use Sandoz Oxycodone CR only for the condition for which it was prescribed.

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

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness.

If you think you have taken too much Sandoz Oxycodone CR, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doss. If you miss one dose, take your next dose at your usual time. You should always try to get back on track with your regular dosing schedule (e.g., 8 o'clock in the morning and 8 o'clock in the evening). If you miss several doses in succession, talk to your doctor before restarting your medication.

Discontinuation:

You should not stop taking Sandoz Oxycodone CR all at once if you have been taking it for more than a few days.

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

Refilling Prescriptions for Sandoz Oxycodone CR:

A new written prescription is required from your doctor each time you need more Sandoz Oxycodone CR . Therefore, it is important that you contact your doctor before your current supply runs out.

What are possible side effects from using Sandoz Oxycodone CR?

These are not all the possible side effects you may feel when taking Sandoz Oxycodone CR. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness,
- Dizziness,
- Dry mouth
- Nausea and/or vomiting,

- Headache
- Problems with vision
- Lack of muscle strength
- Itching
- Sweating
- Constipation

Talk with your doctor or pharmacist about ways to prevent constipation when you start using Sandoz Oxycodone CR.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin.			✓
Respiratory Depression: Slow, shallow or weak breathing.			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular heartbeat: heart palpitations.		✓	
Low Blood Pressure: dizziness, fainting, light-headedness.	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15° and 30°C.

Keep unused or expired Sandoz Oxycodone CR in a secure place to prevent theft, misuse or accidental exposure.

Keep Sandoz Oxycodone CR under lock, out of sight and reach of children and pets.

Disposal:

Sandoz Oxycodone CR should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about Sandoz Oxycodone CR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.sandoz.com or by calling 1-800-361-3062 Or by e-mail at : medinfo@sandoz.com

This leaflet was prepared by Sandoz Canada Inc.

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