

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OXYCODONE HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for OXYCODONE HYDROCHLORIDE TABLETS.

OXYCODONE HYDROCHLORIDE tablets, for oral use, CII Initial U.S. Approval: 1950

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

- See full prescribing information for complete boxed warning.
- Oxycodone hydrochloride tablets expose users to risks of addiction, abuse, and misuse, which may lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)
- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation Mitigation Strategy (REMS) for these products. (5.2)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.3)
- Accidental ingestion of oxycodone hydrochloride tablets, especially by children, can result in a fatal overdose of oxycodone. (5.3)
- Prolonged use of oxycodone hydrochloride tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone from oxycodone hydrochloride tablets. (5.5, 7, 12.3)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)

RECENT MAJOR CHANGES

Boxed Warning	09/2018
Warnings and Precautions (5.2)	09/2018

INDICATIONS AND USAGE

Oxycodone hydrochloride tablets are an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve oxycodone hydrochloride tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or non-opioid combination products):
- Have not been tolerated, or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

DOSEAGE AND ADMINISTRATION-

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)

FULL PRESCRIBING INFORMATION: CONTENTS*

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2.3 Titration and Maintenance of Therapy

Individually titrate oxycodone hydrochloride tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving oxycodone hydrochloride tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see Warnings and Precautions (5.1)]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the oxycodone hydrochloride tablets dosage. If unresponsive opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Discontinuation of Oxycodone Hydrochloride Tablets

When a patient who has been taking oxycodone hydrochloride tablets regularly and may be physically dependent no longer requires therapy with oxycodone hydrochloride tablets, taper the dose gradually, and advise the patient of the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence (9)]. Signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue oxycodone hydrochloride tablets in a physically-dependent patient [see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.3)].

3 DOSEAGE FORMS AND STRENGTHS

Oxycodone Hydrochloride Tablets, USP:

- 5 mg tablets are white to off-white, round, biconvex tablets debossed and bisected with "n" above "20" below on one side and plain on the other side.
- 10 mg tablets are gray, round, biconvex tablets debossed and bisected with "n" above "25" below on one side and plain on the other side.
- 15 mg tablets are green, round, biconvex tablets debossed and bisected with "n" above "21" below on one side and plain on the other side.
- 20 mg tablets are pink, round, biconvex tablets debossed and bisected with "n" above "27" below on one side and plain on the other side.
- 30 mg tablets are blue, round, biconvex tablets debossed and bisected with "n" above "23" below on one side and plain on the other side.

4 CONTRAINDICATIONS

Oxycodone hydrochloride tablets are contraindicated in patients with:

- Significant respiratory depression [see Warnings and Precautions (5.3)].
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment or hypercarbia [see Warnings and Precautions (5.7)].
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see Warnings and Precautions (5.11)].
- Known hypersensitivity (e.g., anaphylaxis) to oxycodone [see Warnings and Precautions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Oxycodone hydrochloride tablets contain oxycodone, a Schedule II controlled substance. As an opioid, oxycodone hydrochloride tablets exposes users to the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence (9)]. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxycodone hydrochloride tablets. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing oxycodone hydrochloride tablets, and monitor all patients receiving oxycodone hydrochloride tablets for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as oxycodone hydrochloride tablets, but use in such patients necessitates intensive counseling about the risks and proper use of oxycodone hydrochloride tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing oxycodone hydrochloride tablets. Strategies for addressing these risks are discussed in prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drugs [see Patient Counseling Information (17)]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to enroll in the program. [see Warnings and Precautions (5.2)].

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are dispensed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, 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 [see Overdosage (10)]. 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 oxycodone hydrochloride tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of oxycodone hydrochloride tablets.

To reduce the risk of respiratory depression, proper dosing and titration of oxycodone hydrochloride tablets are essential [see Dosage and Administration (2)]. Overestimating the oxycodone hydrochloride tablets dosage when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of oxycodone hydrochloride tablets, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of oxycodone hydrochloride tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, similar to opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage as advised accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Use in Specific Populations (8.1), Patient Counseling Information (17)].

5.5 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of oxycodone hydrochloride tablets with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and increase the risk of respiratory depression, which may be life-threatening. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in oxycodone hydrochloride tablets-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using oxycodone hydrochloride tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in oxycodone hydrochloride tablets-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of oxycodone hydrochloride tablets until stable drug effects are achieved [see Drug Interactions (7)].

Concomitant use of oxycodone hydrochloride tablets with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy, or possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using oxycodone hydrochloride tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see Drug Interactions (7)].

5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of oxycodone hydrochloride tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacologic properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Drug Interactions (7)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when oxycodone hydrochloride tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate dangerous machinery until safe effects are achieved. If an adverse reaction is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. When the patient off of the opioid to avoid adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.7 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of oxycodone hydrochloride tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease. Oxycodone hydrochloride tablets-treated patients with significant chronic obstructive pulmonary disease or other pulmonary disease and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of oxycodone hydrochloride tablets [see Warnings and Precautions (5.3)].

Elderly, Cachectic, or Debilitated Patients. Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see Warnings and Precautions (5.3)].

Monitor patients closely, particularly when initiating and titrating oxycodone hydrochloride tablets and when oxycodone hydrochloride tablets are given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.3)]. Alternatively, consider the use of non-opioid analgesics.

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. When the patient off of the opioid to avoid adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

Oxycodone hydrochloride tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients who are unable to maintain blood pressure because of a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see Drug Interactions (7)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of oxycodone hydrochloride tablets. In patients with circulatory shock, oxycodone hydrochloride tablets may cause vasoconstriction and may further reduce cardiac output and blood pressure. Avoid use of oxycodone hydrochloride tablets in patients with circulatory shock.

5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), oxycodone hydrochloride tablets may reduce the respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with oxycodone hydrochloride tablets.

Opioids may obscure the clinical course in a patient with a head injury. Avoid the use of oxycodone hydrochloride tablets in patients with impaired consciousness.

5.11 Risks of Use in Patients with Gastrointestinal Conditions

Oxycodone hydrochloride tablets are contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

The oxycodone in oxycodone hydrochloride tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in oxycodone hydrochloride tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other seizure disorders associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during oxycodone hydrochloride tablets therapy.

5.13 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including oxycodone hydrochloride tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [see Drug Interactions (7)].

When discontinuing oxycodone hydrochloride tablets in a physically-dependent patient, gradually taper the dosage [see Dosage and Administration (2.4)]. Do not abruptly discontinue oxycodone hydrochloride tablets in these patients [see Drug Abuse and Dependence (9.3)].

5.14 Risks of Driving and Operating Machinery

Oxycodone hydrochloride tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of oxycodone hydrochloride tablets and know how they will react to the medication [see Patient Counseling Information (17)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse [see Warnings and Precautions (5.1)]
- Life-Threatening Respiratory Depression [see Warnings and Precautions (5.3)]
- Neonatal Opioid Withdrawal Syndrome [see Warnings and Precautions (5.4)]
- Interactions with Benzodiazepines or Other CNS Depressants [see Warnings and Precautions (5.6)]
- Adrenal Insufficiency [see Warnings and Precautions (5.8)]
- Severe Hypotension [see Warnings and Precautions (5.9)]
- Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.11)]
- Seizures [see Warnings and Precautions (5.12)]
- Withdrawal [see Warnings and Precautions (5.13)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Oxycodone hydrochloride tablets have been evaluated in open label clinical trials in patients with cancer and nonmalignant pain. Oxycodone hydrochloride tablets have been associated with adverse experiences similar to those seen with other opioids. Serious adverse reactions associated with oxycodone hydrochloride tablets include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock.

The common adverse reactions seen on initiation of therapy with oxycodone hydrochloride tablets are dose related and are typical opioid-related adverse reactions. The most frequent of these included nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence. The frequency of these reactions depends on several factors, including clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual.

In all patients for whom dosing information was available (n=191) from the open-label and double-blind studies involving oxycodone hydrochloride tablets, the most common adverse reactions were respiratory depression, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence. The frequency of these reactions depends on several factors, including clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual.

Other less frequently observed adverse reactions from opioid analgesics, including oxycodone hydrochloride tablets included: Blood and lymphatic system disorders: anemia, leukopenia

Cardiac disorders: cardiac failure, palpitation, tachycardia

Gastrointestinal disorders: abdominal pain, dry mouth, diarrhea, dyspepsia, dysphagia, glossitis, nausea, vomiting

General disorders and administration site conditions: chills, edema, edema peripheral, pain, pyrexia

Immune system disorders: hypersensitivity

Infections and infestations: bronchitis, gingivitis, infection, pharyngitis, rhinitis, sepsis, sinusitis, urinary tract infection

Injury, poisoning and procedural complications: injury

Metabolism and nutrition disorders: decreased appetite, gout, hyperglycemia

Musculoskeletal and connective tissue disorders: arthralgia, arthritis, back pain, bone pain, myalgia, neck pain, pathological fracture

Nervous system disorders: hyperreflexia, hypoesthesia, migraine, neuralgia, tremor, vasodilation

Psychiatric disorders: agitation, anxiety, confusional state, nervousness, personality disorder

Respiratory, thoracic and mediastinal disorders: cough, dyspnea, epistaxis, laryngospasm, lung disorder

Skin and subcutaneous tissue disorders: photosensitivity reaction, rash, hyperhidrosis, urticaria

Vascular disorders: thrombophlebitis, hemorrhage, hypotension, vasodilation

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of oxycodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General disorders and administrative site disorders: drug withdrawal syndrome neonatal [see Warnings and Precautions (5.4)]

Respiratory, thoracic and mediastinal disorders: pharyngeal edema

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs [see Drug Interactions (7)].

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use [see Warnings and Precautions (5.8)].

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in oxycodone hydrochloride tablets [see Contraindications (4)].

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see Clinical Pharmacology (12.2)].

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with oxycodone hydrochloride tablets.

Table 1: Clinically Significant Drug Interactions with oxycodone hydrochloride tablets

Inhibitors of CYP3A4 and CYP2D6

Clinical Impact: The concomitant use of oxycodone hydrochloride tablets and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of oxycodone hydrochloride tablets and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of oxycodone hydrochloride tablets is achieved [see Warnings and Precautions (5.5)]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease [see Clinical Pharmacology (12.3)], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.

Intervention: If concomitant use is necessary, consider dosage reduction of oxycodone hydrochloride tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.

If a CYP3A4 inhibitor is discontinued, consider increasing the oxycodone hydrochloride tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider oxycodone hydrochloride tablets dosage reduction and monitor for signs of respiratory depression.

Examples: Rifampin, carbamazepine, phenytoin

Benzodiazepines and Other Central Nervous System (CNS) Depressants

Clinical Impact: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Intervention: Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Warnings and Precautions (5.6)].

Examples: Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

Serotonergic Drugs

Clinical Impact: The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see Adverse Reactions (6.2)].

Medication Guide

Oxycodone Hydrochloride (ox" i koe' done hye" droe klor' ide) Tablets USP, CII

Oxycodone Hydrochloride Tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require an opioid pain medicine, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about oxycodone hydrochloride tablets:

- Get emergency help right away if you take too much oxycodone hydrochloride tablets (overdose).** When you first start taking oxycodone hydrochloride tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking oxycodone hydrochloride tablets with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your oxycodone hydrochloride tablets. They could die from taking it

• Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with oxycodone hydrochloride tablets may cause you to overdose and die.

The possible side effects of oxycodone hydrochloride tablets are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of oxycodone hydrochloride tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov

Manufactured by:
Novel Laboratories, Inc.
Somerset, NJ 08873

Manufactured For:
Lupin Pharmaceuticals, Inc.
Baltimore, MD 21202

PI4310000201
Iss. 10/2019

This Medication Guide has been approved by the
U.S. Food and Drug Administration.

Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue oxycodone hydrochloride tablets if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions</i> (5.3)].
Intervention:	The use of oxycodone hydrochloride tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
	If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of oxycodone hydrochloride tablets and/or may precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of oxycodone hydrochloride tablets and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant risk of anticholinergic drugs may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when oxycodone hydrochloride tablets are used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions* (5.4)]. Available data with oxycodone hydrochloride tablets in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. Animal reproduction studies with oral administrations of oxycodone HCl in rats and rabbits during the period of organogenesis at doses 2.6 and 8.1 times, respectively, the human dose of 60 mg/day did not reveal evidence of teratogenicity or embryo-fetal toxicity. In several published studies, treatment of pregnant rats with oxycodone at clinically relevant doses and below, resulted in neurobehavioral effects in offspring [see *Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents 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 use, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see *Warnings and Precautions* (5.4)].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Oxycodone hydrochloride tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including oxycodone hydrochloride tablets, can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of oxycodone HCl administered during the period of organogenesis up to 16 mg/kg/day and up to 25 mg/kg/day, respectively. These studies revealed no evidence of teratogenicity or embryo-fetal toxicity due to oxycodone. The highest doses tested in rats and rabbits were equivalent to approximately 2.6 and 8.1 times an adult human dose of 60 mg/day, respectively, on a mg/m² basis. In published studies, offspring of pregnant rats administered oxycodone during gestation have been reported to exhibit neurobehavioral effects including altered stress responses, increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Prenatal Day 1, 3, and 5; 0.3 times an adult human dose of 60 mg/day, on a mg/m² basis) and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human dose of 60 mg/day, on a mg/m² basis).

8.2 Lactation

Risk Summary

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse effects. Lactation studies have not been conducted with oxycodone hydrochloride tablets, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for oxycodone hydrochloride tablets and any potential adverse effects on the breastfed infant from oxycodone hydrochloride tablets or from the underlying maternal condition.

Clinical Considerations

Infants exposed to oxycodone hydrochloride tablets through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see *Adverse Reactions* (6.2), *Clinical Pharmacology* (12.2)].

8.4 Pediatric Use

The safety and efficacy of oxycodone hydrochloride tablets in pediatric patients have not been evaluated.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of oxycodone hydrochloride tablets, 20.8% (112/538) were 65 and over, while 7.2% (39/538) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients (aged 65 years or older) may have increased sensitivity to oxycodone. In general, use caution when selecting a dosage for an elderly patient, 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.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of oxycodone hydrochloride tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see *Warnings and Precautions* (5.7)].

Oxycodone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Because oxycodone is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Initiate therapy in these patients with a lower than usual dosage of oxycodone hydrochloride tablets and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see *Clinical Pharmacology* (12.3)].

8.7 Renal Impairment

Because oxycodone is known to be substantially excreted by the kidney, its clearance may decrease in patients with renal impairment. Initiate therapy with a lower than usual dosage of oxycodone hydrochloride tablets and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see *Clinical Pharmacology* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Oxycodone hydrochloride tablets contain oxycodone, a Schedule II controlled substance.

9.2 Abuse

Oxycodone hydrochloride tablets contain oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone hydromorphone, methadone, morphine, oxymorphone, and tapentadol. Oxycodone hydrochloride tablets can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions* (5.1)].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Oxycodone hydrochloride tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of Oxycodone Hydrochloride Tablets

Oxycodone hydrochloride tablets is for oral use only. Abuse of oxycodone hydrochloride tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of oxycodone hydrochloride tablets with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene, mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Oxycodone hydrochloride tablets should not be abruptly discontinued in a physically-dependent patient [see *Dosage and Administration* (2.4)]. If oxycodone hydrochloride tablets are abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see *Use in Specific Populations* (8.1)].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with oxycodone hydrochloride tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see *Clinical Pharmacology* (12.2)].

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of oxycodone in oxycodone hydrochloride tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

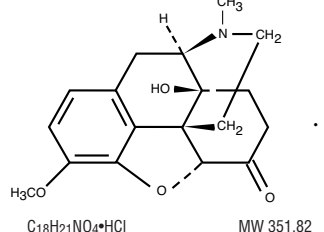
11 DESCRIPTION

Oxycodone hydrochloride tablets, USP contain oxycodone, an opioid agonist.

Each tablet for oral administration contains 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg, of oxycodone hydrochloride USP.

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methyl-17-methylmorphinan-6-one hydrochloride and has the following structural formula:



The tablets contain the following inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and magnesium stearate.

Apart from the above ingredients, 10 mg tablet contains lake blend LB-1171 (gray powder), 15 mg tablet contains lake blend LB-451 (green), 20 mg tablet contains lake blend LB-1635 (pink powder) and 30 mg tablet contains lake blend LB-105000 (blue powder).

The 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablets contain the equivalent of 4.5 mg, 9.0 mg, 13.5 mg, 18.0 mg and 27.0 mg, respectively, of oxycodone free base.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

Effects on Central Nervous System

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

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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on Cardiovascular System

Oxycodone produces peripheral vasodilatation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see *Adverse Reactions* (6.2)]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see *Adverse Reactions* (6.2)].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent analgesic concentration of oxycodone for an individual patient may increase with oxycodone for an 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 [see *Dosage and Administration* (2.1, 2.3)].

Concentration-Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration 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 adverse reactions [see *Dosage and Administration* (2.1, 2.2, 2.3)].

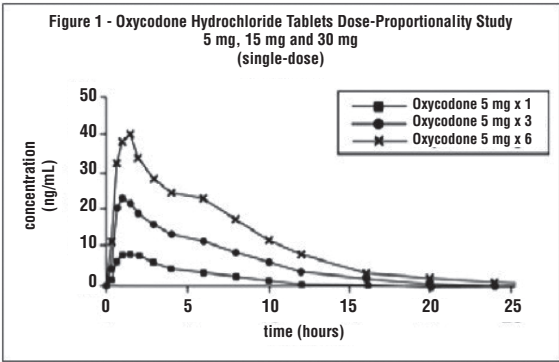
12.3 Pharmacokinetics

The activity of oxycodone hydrochloride tablets is primarily due to the parent drug oxycodone. Oxycodone hydrochloride tablets are designed to provide immediate release of oxycodone.

Table 2: Pharmacokinetic Parameters (Mean±SD)						
Dose/Parameters	AUC (ng·hr/mL)	C _{max} (ng/mL)	T _{max} (hr)	C ₉₀ (ng/mL)	C ₉₅ (ng/mL)	Half-Life (hr)
Single Dose Pharmacokinetics						
Oxycodone Hydrochloride Tablets 5 mg tabs x 3	133.2±33	22.3±8.2	1.8±1.8	n/a	n/a	3.73±0.9
Oxycodone Hydrochloride Tablets 15 mg oral solution	128.2±35.1	22.2±7.6	1.4±0.7	n/a	n/a	3.55±1.0
Oxycodone Hydrochloride Liquid Concentrate 15 mg oral solution	130.6±34.7	21.1±6.1	1.9±1.5	n/a	n/a	3.71±0.8
Oxycodone Hydrochloride Tablets 30 mg tab	268.2±60.7	39.3±14.0	2.6±3.0	n/a	n/a	3.85±1.3
Food-Effect, Single Dose						
Oxycodone Hydrochloride 10 mg/10 mL oral sol'n (fasted)	105±6.2	19.0±3.7	1.25±0.5	n/a	n/a	2.9±0.4
Oxycodone Hydrochloride 10 mg/10 mL oral sol'n (fed)	133±25.2	17.7±3.0	2.54±1.2	n/a	n/a	3.3±0.5
Multiple-Dose Studies						
Oxycodone Hydrochloride Tablets 5 mg tabs q6h x 14 doses	113.3±24.0	15.7±3.2	1.3±0.3	7.4±1.8	9.4±2.0	n/a
Oxycodone Hydrochloride 3.33 mg (3.33 mL) oral sol'n q4h x 21 doses	99.0±24.8	12.9±3.1	1.0±0.3	7.2±2.3	9.7±2.6	n/a

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison to a parenteral dose. This high oral bioavailability (compared to other oral opioids) is due to lower presystemic and/or first-pass metabolism of oxycodone. The relative oral bioavailability of oxycodone hydrochloride 15 mg and 30 mg tablets, compared to the 5 mg oxycodone hydrochloride tablets, is 96% and 101%, respectively. Oxycodone hydrochloride 15 mg tablets are bioequivalent to the 5 mg oxycodone hydrochloride tablets (see Table 2 for pharmacokinetic parameters). Dose proportionality of oxycodone has been established using the oxycodone hydrochloride 5 mg tablets at doses of 5 mg, 15 mg (three 5 mg tablets) and 30 mg (six 5 mg tablets) based on extent of absorption (AUC) (see Figure 1). It takes approximately 18 to 24 hours to reach steady-state plasma concentrations of oxycodone with oxycodone hydrochloride tablets.



Food Effect

A single-dose food effect study was conducted in normal volunteers using the 5 mg/5 mL solution. The concurrent intake of a high fat meal was shown to enhance the extent (27% increase in AUC), but not the rate of oxycodone absorption from the oral solution (see Table 2). In addition, food caused a delay in T_{max} (1.25 to 2.54 hour). Similar effects of food are expected with the 15 mg and 30 mg tablets.

Distribution
Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk [see *Special Populations* (8.2)].

Elimination

Metabolism

A high portion of oxycodone is N-dealkylated to noroxycodone during first-pass metabolism, and is catalyzed by CYP3A4. Oxymorphone is formed by the O-demethylation of oxycodone. The metabolism of oxycodone to oxymorphone is catalyzed by CYP2D6 [see *Drug Interactions* (7)]. Free and conjugated noroxycodone, free and conjugated oxycodone, and oxymorphone are excreted in human urine following a single oral dose of oxycodone. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Oxymorphone is present in the plasma only in low concentrations. The analgesic activity profile of other metabolites is not known at present.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The plasma clearance was 0.8 L/min for adults. Apparent elimination half-life of oxycodone following the administration of oxycodone hydrochloride tablets was 3.5 to 4 hours.

Specific Populations

Age: Geriatric Population

Population pharmacokinetic studies conducted with oxycodone hydrochloride tablets, indicated that the plasma concentrations of oxycodone did not appear to be increased in patients over the age of 65.

Hepatic Impairment

In a clinical trial supporting the development of oxycodone hydrochloride tablets, too few patients with decreased hepatic function were evaluated to study these potential differences. However, because oxycodone is extensively metabolized in the liver, its clearance may decrease in hepatic impaired patients [see *Use in Specific Populations* (8.6)].

Renal Impairment

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function [see *Use in Specific Populations* (8.7)].

13 NONCLINICAL TOXICOLOGY