Drug Monograph

Generic Name: oxycodone hydrochloride
Trade Name: Oxaydo®
Dosage Form: 5 mg, 7.5 mg Tablets
National Drug Codes (NDC#) 5 mg 69344-113-11, 7.5 mg 69344-213-11
Manufacturer: Egalet US Inc.
ADF Product Classification: Aversion

Executive Summary

Oxaydo® (oxycodone hydrochloride [HCl]), previously known as Oxecta®, is being evaluated by the Drug Formulary Commission for consideration of inclusion on the Massachusetts formulary of therapeutically equivalent substitutions, as outlined in Chapter 258 of the Acts of 2014. This agent is an immediate-release (IR) formulation of oxycodone HCl that was originally Food and Drug Administration (FDA)-approved in 2011 for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate. The recommended initial dose of Oxaydo® (oxycodone HCl) for patients that are opioid naïve is in a range of 5 mg to 15 mg every four to six hours as needed for pain. The manufacturer does not provide specific conversion factors for patients converting from other opioid to Oxaydo® (oxycodone HCl). Oxycodone HCl is a pure opioid agonist that is relatively selective for the μ opioid receptor; however, at higher doses activity at other opioid receptors is possible. Similar to various other opioid analgesics, it is designated as a Schedule II controlled substance.[1,2]

According to the manufacturer, Oxaydo® is the first IR formulation of oxycodone HCl to utilize technology (AVERSION® Technology) targeted to discourage common tampering practices associated with opioid misuse; however, the prescribing information does state that this product may be abused similar to other opioids, including crushing, chewing, snorting, and/or injecting the product.[1,2] Information on this specific abuse-deterring technology states that attempts to extract the active ingredient using solvents converts the tablet into a viscous gelatinous mixture that prevents injection of the medication. In addition, an inactive ingredient that was added to Oxaydo® (oxycodone HCl) is thought to discourage abuse associated with snorting as it causes burning and irritation to nasal passages.[3]

The FDA approval of this agent was based upon evaluations of the previously established safety and efficacy for Roxicodone® (oxycodone HCl) tablets. No trials are listed in the Clinical Studies section of the package insert. However, there was one double-blind, active-comparator, crossover study of 40 nondependent recreational opioid users that was included in the Drug Abuse and Dependence section. This study evaluated the subjective and physiologic effects of the intranasal administration of IR Roxicodone® (oxycodone HCl) compared to IR Oxaydo® (oxycodone HCl). In summary, the Overall Drug Liking and Take Drug Again subject responses were significantly less favorable with the crushed formulation of Oxaydo® (oxycodone HCl) with subjects experiencing more nasal-related symptoms with this agent compared to Roxicodone® (oxycodone HCl).[4] As reported by the manufacturer, the clinical significance of the difference in drug liking and difference in response to taking the drug again reported in this study has not yet been established. There is currently no evidence that Oxaydo® (oxycodone HCl) has a reduced abuse liability compared to immediate-release oxycodone.[1,2]

There is currently a lack of published post-marketing data evaluating if Oxaydo® (oxycodone HCl) is abused less frequently in the community. The FDA will require an epidemiological study to address whether Oxaydo® (oxycodone HCl) results in a decrease in misuse and abuse, and the consequences of misuse and abuse. The original timetable for submission of the final report for the epidemiological study was June 2016; however, it is not clear if the timetable is still valid due to the sale of the original product to Egalet.[5] Oxaydo® (oxycodone HCl) is not currently subject to any Risk Evaluation and Mitigation Strategies (REMS) program.[6]

Reference Data

Oxycodone HCl is a pure opioid agonist that is relatively selective for the μ opioid receptor. It can, however, bind to other opioid receptors at higher doses. Although the precise mechanism of action is unknown, specific central nervous system (CNS) opioid receptors for endogenous compounds with morphine-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.[1,2] In addition to the analgesic effect, the binding of Oxaydo® (oxycodone HCl) to μ receptors produces a variety of other potential unwanted side effects including bradycardia, sedation, euphoria, physical dependence, and potentially respiratory depression.[1,2]

This agent joins multiple other short-acting opioids available on the market; however, as of now Oxaydo® (oxycodone HCl) is the only agent presently available with aversion technology.[2] A list of these medications is shown below in Table1.

Table 1. Short-Acting Opioid Availability[2]

Generic Name (Trade name)	Abuse Deterrent Formulation Available	Commercially Available
Single-Agent Analgesics		
Codeine*	-	✓
Fentanyl (Abstral®, Actiq®, Fentora®, Lazanda®, Sublimaze®, Subsys®)	-	✓
Hydromorphone (Dilaudid®, Dilaudid HP®)	-	✓
Meperidine (Demerol®)	-	✓
Morphine (Duramorph®, Infumorph®, MSIR®)	-	✓
Oxycodone (Roxicodone®)	-	✓
Oxycodone (Oxaydo®)	✓	✓
Oxymorphone (Opana®)	-	✓
Tapentadol (Nucynta®)	-	✓
Combination Analgesics		
Codeine/acetaminophen (Tylenol with codeine 2®, Tylenol with codeine 3®, Tylenol with codeine 4®)*	-	✓
Codeine/acetaminophen/Butalbital/ Caffeine/	-	✓
Codeine/aspirin/Butalbital/Caffeine (Ascomp® with codeine, Fiorinal® with codeine)	-	✓
Codeine/aspirin/carisoprodol	-	✓
dihydrocodeine/acetaminophen/caffeine (Trezix®)	-	✓
dihydrocodeine/aspirin/caffeine (Synalgos-DC®)	-	✓
Hydrocodone/acetaminophen (Hycet®, Lortab®, Norco®, Vicodin®, Vicodin ES®, Vicodin HP®, Xodol®, Zamicet®)	-	✓
Hydrocodone/ibuprofen (Ibudone®, Reprexain®)	-	✓
Oxycodone/acetaminophen (Endocet®, Magnacet®, Percocet®, Primlev®, Xartemis XR®, Xolox®)	-	✓
Oxycodone/aspirin (Endodan®)	-	✓

Generic Name (Trade name)	Abuse Deterrent Formulation Available	Commercially Available
oxycodone/ibuprofen (Ibudone®, Vicoprofen®)	-	✓

*Antitussive agents containing codeine are excluded from this table.

Therapeutic Indications/Efficacy

Oxaydo® (oxycodone HCl) is indicated for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate. There are no published clinical trials specifically evaluating the safety and efficacy of oxycodone HCl (Oxecta® or Oxaydo®). According to the manufacturer, the analgesic efficacy of these agents was established by previous evaluations of efficacy and safety for Roxicodone® (oxycodone HCl) tablets.[1]

Currently this agent is marketed as the first and only IR oxycodone that discourages intranasal abuse due to the addition of an inactive excipient that creates nasal discomfort and irritation if product is crushed and snorted.[7] The FDA allowed the company to include results from a "drug-liking" study in its package insert under the Drug Abuse section (9.2). However, it also was instructed to include a disclaimer that there is no evidence that Oxaydo® (oxycodone HCl) has a reduced abuse liability compared to IR oxycodone.

This study was a single-center, single-dose, randomized, double-blind, active-controlled two-way crossover trial that enrolled 40 adult, nondependent, recreational opioid users. Subjects self-administered a single dose of each treatment intranasally (immediate-release oxycodone [IRO] and immediate-release Oxecta® [IRO-A]) in order to compare the Drug Liking visual analog scale (VAS) maximum effect (E_{max}), Overall Drug Liking effect at eight hours (E_{8h}) and Take Drug Again effect at eight hours(E_{8h}). In summary, a significant difference was found for all endpoints with more individuals preferring the IRO to IRO-A ($P<0.0001$). In addition, more nasal-related adverse events were reported with the administration of IRO-A. Other adverse events were similar between the two agents.[4] Results are outlined in Table 2.

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Schoedel et al[4] Crushed Oxecta® (oxycodone HCl) 15 mg vs crushed Roxicodone® (oxycodone HCl) 15 mg)	AC, DB, RCT, XO Subjects 18 to 55 years of age who were nondependent, recreational opioid users	N=40 Single dose	Primary: E_{max} for Drug Liking and E_{8h} postdose for Take Drug Again and Overall Drug Liking Secondary: VAS endpoints, pupillometry and subject-rated scales for nasal effects	Primary: Thirty-nine of the 40 subjects that were randomized had evaluable results. The last subject was excluded due to postdose vomiting. Least squares mean Drug Liking VAS E_{max} (70.8 vs 93.5), Overall Drug Liking E_{8h} (47.8 vs 87.4) and Take Drug Again E_{8h} (45.9 vs 91.3) were significantly lower for crushed Oxecta® (oxycodone HCl) compared to crushed Roxicodone® (oxycodone HCl) (all P<0.0001). Thirty percent of subjects exposed to crushed Oxecta® (oxycodone HCl) responded that they would not take the drug again compared to 5% of subjects exposed to immediate-release oxycodone. P value not reported. Secondary: Pupillary responses between treatments were similar overall, but differences were noted for some endpoints/time points. Subjects experienced more nasal-related symptoms and facial adverse events with the crushed Oxecta® (oxycodone HCl). In addition, 21 of 40 subjects had a decreased ability to completely insufflate two crushed Oxecta® (oxycodone HCl) tablets within a fixed time period.

Drug regimen abbreviation: Q12H=every 12 hours
Study abbreviations: AC=active-controlled, DB=double-blind, E_{max}=maximum effect, E_{8h}=effect at eight hours, IRO=immediate-release oxycodone (Roxicodone®), IRO-A=immediate-release oxycodone (Oxecta®), IRO-A with niacin (immediate-release oxycodone with niacin), OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, VAS=visual analog scale

Pharmacokinetics/Pharmacogenomics

Absorption
The oral bioavailability of oxycodone is 60 to 87%. The high oral bioavailability of oxycodone HCl compared to other oral opioids is due to lower pre-systemic and/or first-pass metabolism of oxycodone. The time to peak plasma concentration (T_{max}) of Oxaydo® (oxycodone HCl) occurred within 1.2 to 1.4 hours after administration of the first dose under fasted conditions. Peak plasma concentration (C_{max}) and exposure (AUC) are proportional with the dose. Oxaydo® (oxycodone HCl) is bioequivalent with standard oxycodone immediate-release. Administration of Oxaydo® (oxycodone HCl) with food causes a delay in T_{max} to a range of 1.25 to 3.00 hours. This is not considered clinically relevant.[1,2] The T_{max} of crushed or otherwise tampered with tablets of Oxaydo® (oxycodone HCl) has not been published.

Distribution
Following intravenous administration, the volume of distribution for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone is approximately 45%. Oxycodone HCl has been known to distribute in human breast milk.[1,2]

Metabolism
Oxycodone HCl is extensively metabolized by multiple metabolic pathways to product noroxycodone, oxymorphone, and noroxymorphone, which subsequently undergo glucuronidation. CYP 3A4 mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with less contribution from CYP 2D6 mediated O-demethylation to oxymorphone. The formation of these and related metabolites can be affected by other drugs. Noroxycodone, the major circulating metabolite, has an area under the curve (AUC) ratio of 0.6 relative to that of oxycodone. Noroxycodone is a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects is much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known. [1,2]

Elimination
Oxycodone HCl and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; and conjugated oxymorphone ≤14%. Both free and conjugated noroxycodone have been found in urine but not quantified. The total plasma clearance was 0.8 L/minute among adults. The elimination half-life of oxycodone is 3.5 to 4.0 hours. [1,2]

Pharmacogenomics
There are no specific pharmacogenomics reported for Oxaydo® (oxycodone HCl). However, there has been some literature to date looking at pharmacogenetics with the opioid class. It has been noted that utilizing pharmacogenetics in clinical practice for the context of pain is challenging, due to the complexity of this multifaceted phenotype and the overall subjective nature of pain perception and response to analgesia. Overall, numerous genes involved with the pharmacokinetics and dynamics of opioids response are candidate genes in the context of opioid analgesia. The clinical relevance of *CYP2D6* genotyping to predict analgesic outcomes is still relatively unknown; the two extremes in *CYP2D6* genotype (ultrarapid and poor metabolism) seem to predict pain response and/or adverse effects. Overall, the level of evidence linking genetic variability (*CYP2D6* and *CYP3A4*) to oxycodone response and phenotype (altered biotransformation of oxycodone into oxymorphone and overall clearance of oxycodone and oxymorphone) is strong; however, there has been no randomized clinical trial on the benefits of genetic testing prior to oxycodone therapy.[8]

Special Populations

Table 3. Special Populations[1,2]

Population	Precaution
Elderly	Information available for oxycodone HCl indicates that the plasma

	concentrations of oxycodone HCl did not appear to be increased in patients over the age of 65 years. Elderly patients (≥65 years) may have increased sensitivity to Oxaydo® (oxycodone HCl). Use caution when selecting a dose for an elderly patient, starting at the low end of the dosing range due to the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease(s), and use of other drug therapies.
Renal dysfunction	Information obtained from oxycodone HCl indicate that patients with renal impairment (CrCl <60 mL/minute) had higher plasma concentrations of oxycodone HCl than subjects with normal renal function Available information with oxycodone HCl indicates that patients with renal impairment (CrCl<60 mL/minute) have higher plasma concentrations of oxycodone HCl than subjects with normal renal function. Use conservative approaches to initiate dosing in patients with renal impairment, monitoring closely and adjusting subsequent doses based upon individual clinical response.
Hepatic dysfunction	Since oxycodone HCl is extensively metabolized in the liver, its clearance may be decreased in patients with hepatic impairment. Use conservative approaches to initiate dosing in patients with hepatic impairment, monitoring closely and adjusting subsequent doses based upon individual clinical response.
Pregnancy / nursing	Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Based on limited human data in the literature, oxycodone HCl does not appear to increase the risk of congenital malformations. Use during pregnancy only if clearly necessary and the potential benefits outweigh the potential risks. Opioids cross the placenta and may produce respiratory depression and psycho-physiological effects in neonates; therefore, it is not for use in women during and immediately prior to labor. Monitor closely. Low levels of oxycodone HCl have been detected in maternal milk. The amount of oxycodone HCl delivered to the infant depends on the plasma concentration of the mother, the amount of milk ingested by the infant, and the extent of first-pass metabolism. A decision should be made whether to discontinue nursing or discontinue the drug.
Children	The safety, effectiveness, and pharmacokinetics in individuals less than 18 years of age have not been established.
Gender / Race	Information obtained from oxycodone HCl support the lack of gender effect on the pharmacokinetics of this agent. No race-specific differences in pharmacokinetic data have been identified.

CrCl=creatinine clearance

Dosage Forms

Table 4. Availability, Storage and Handling[1]

Dosage form	Strengths	Special handling or storage
Tablet	5 mg 7.5 mg	Store up to 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Protect from moisture. This product, similar to all opioids, is liable to

Dosage form	Strengths	Special handling or storage
		diversion and misuse by the general public and healthcare workers and must be handled accordingly.

Dosage Range[1-2]

The dose of Oxaydo® (oxycodone HCl) should be individually adjusted according to severity of pain, and the patient's response, weight, age, and prior analgesic treatment experience.

Initiation of Therapy:
Patients who have not been receiving opioid analgesics should be started on Oxaydo® (oxycodone HCl) in a dosing range of 5 mg to 15 mg every four to six hours as needed for pain. The dose should be titrated based upon the individual patient's response to their initial dose of Oxaydo® (oxycodone HCl).

Patients with chronic pain may need to be dosed at the lowest dosage level that will achieve acceptable analgesia and tolerable adverse reactions, on an around-the-clock basis rather than on an as needed basis.

Conversion to Oxaydo® (oxycodone HCl):

Conversion from Fixed-Ratio Oral Opioid/Non-Opioid Combinations

When converting patients from fixed-ratio opioid/non-opioid drug regimens to Oxaydo® (oxycodone HCl), determine whether or not to continue the non-opioid analgesic. The dose of Oxaydo® (oxycodone HCl) should be titrated in response to the level of analgesia and adverse reactions afforded by the dosing regimen regardless of whether the non-opioid is continued.

Conversion from Other Oral Opioid Therapy to Oxaydo® (oxycodone HCl)

If a patient has been receiving opioid-containing medications prior to taking Oxaydo® (oxycodone HCl), factor the potency of the prior opioid relative to oxycodone HCl into the selection of the total daily dose of oxycodone HCl.

In converting patients from other opioids to Oxaydo® (oxycodone HCl), close observation and adjustment of dosage based upon the patient's response to is necessary.

Maintenance of Therapy:
Continual re-evaluation of the patient receiving Oxaydo® (oxycodone HCl) is important, with special attention to the maintenance of pain management and the relative incidence of adverse reactions associated with therapy. If the level of pain increases, efforts should be made to identify the source of the increased pain, while adjusting the dose as described above to decrease the level of pain.

During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), the continued need for the use of opioid analgesics must be re-assessed as appropriate.

Hepatic Insufficiency
Since oxycodone HCl is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Dose initiation in such patients should follow a conservative approach and dose adjustments should be made according to the clinical situation.

Renal Insufficiency

Published data reported that elimination of oxycodone HCl was impaired in patients with end-stage renal failure. The mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance.

Dose initiation in such patients should follow a conservative approach and dose adjustments should be made according to the clinical situation.

Geriatric Patients
Elderly patients (aged 65 years or older) may have increased sensitivity to Oxaydo® (oxycodone HCl). Use caution when selecting a dose 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, concomitant disease, and use of other drug therapy.

Special considerations
Oxaydo® (oxycodone HCl) must be swallowed whole with enough water to ensure complete swallowing immediately after placing in the mouth. This agent should not be crushed or administered via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes. This product can be taken with or without food.

Discontinuation of Therapy:
When the decision is made to discontinue therapy, it is important to gradually taper the Oxaydo® (oxycodone HCl) over time to prevent the development of an opioid abstinence syndrome (narcotic withdrawal). In general, therapy can be decreased by 25 to 50% per day with careful monitoring for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, the dose should be raised to the previous level and tapered more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both.

Precautions

Table 5. Warnings/Precautions[1,2]

Warnings/ Precautions	Respiratory depression; the primary risk with the use of this product is respiratory depression and occurs more frequently in elderly or debilitated patients, in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, or following large initial doses of opioids given to non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration (e.g., benzodiazepines, tricyclic antidepressants, and sedative hypnotics, etc.). Use with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. Even at therapeutic doses, this agent may decrease respiratory drive to the point of apnea. In these high risk patients, alternative non-opioid analgesics should be considered, and opioids must be employed only under careful medical supervision at the lowest effective dose.
	Misuse and abuse; Oxycodone HCl is a Schedule II controlled substance, which are often sought by drug abusers and people with addiction disorders. This product can be abused in a manner similar to other opioid agonists, legal or illicit. Consider these issues when prescribing or dispensing oxycodone HCl in situations where the physician or pharmacist is concerned about an increased risk of misuse or abuse. This agent may be abused by crushing, chewing, snorting or injecting the product, which poses a significant risk to the abuser that could result in overdose and death. Concerns about abuse and addiction should not prevent the proper management of pain.
	Central nervous system (CNS) depressants; Oxycodone HCl may cause severe hypotension in patients whose ability to maintain blood pressure has been

	compromised by a depleted intravascular volume, or after concurrent administration with drugs such as phenothiazines, general anesthetics or other agents which compromise vasomotor tone. It may also produce orthostatic hypotension in ambulatory patients. Administer with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.
	Gastrointestinal (GI) effects; Do not administer to patients with gastrointestinal obstruction, especially paralytic ileus because oxycodone HCl diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction. Administering this product may obscure the diagnosis or clinical course in patients with acute abdominal condition.
	Pancreatic/biliary tract disease; Use with caution in patients with biliary tract disease, including acute pancreatitis, as oxycodone HCl may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.
	Special risk groups; Use with caution and in reduced dosages in patients with severe renal or hepatic impairment, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients. Exercise caution in the administration of this agent to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens. All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings. Keep out of the reach of children and in cases of accidental ingestion, seek emergency medical help immediately.
	Driving and operating machinery; Opioids may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating heavy machinery. Thoroughly counsel patients on the risks.
	Cytochrome P450 3A4 inhibitors and inducers; Given the metabolic pathway of oxycodone HCl, drugs that alter CYP 3A4 activity may cause changes in clearance of oxycodone HCl which could lead to changes in oxycodone plasma concentrations. CYP 3A4 inhibitors may lead to an increase in oxycodone plasma concentrations and possibly increased or prolonged opioid effects. CYP 3A4 inducers may 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 HCl. If co-administration is necessary, caution is advised when initiating oxycodone HCl treatment in patients currently taking or discontinuing CYP 3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Contraindications

Oxaydo® (oxycodone) is contraindicated in patients with respiratory depression in an unmonitored setting or in the absence of resuscitative equipment, known or suspected paralytic ileus, acute or severe bronchial asthma or hypercarbia, or hypersensitivity to oxycodone, oxycodone salts, or any other ingredients in the product.[1,2]

Adverse Drug Events

Based upon the information available from the patients (n=191) treated with oxycodone HCl in open-label and double-blind trials, the adverse events reported in ≥3% of individuals in descending order of frequency included: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.[1,2]

Drug Interactions

Table 6. Drug and Food Interactions[1,2]

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
Naltrexone	Contraindicated	Concomitant use will result in precipitation of opioid withdrawal symptoms and decreased opioid effectiveness.
Alcohol (ethanol)	Major	Concomitant use may result in increased central nervous system (CNS) and/or respiratory depression. Counsel patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol.
CNS Depressants (e.g., sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, alcohol, etc.)	Major	Concomitant use may increase the risk of respiratory depression, profound sedation, or coma. Use oxycodone HCl with caution and in reduced dosages in patients taking these agents. Patients should not consume alcohol or any medications containing alcohol while taking opioids.
Muscle Relaxants	Major	May result in enhanced neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Mixed Agonist/Antagonist (pentazocine, nalbuphine, & butorphanol) and Partial Agonist (e.g., buprenorphine) Opioid Analgesics	Major	Do not administer to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic, including oxycodone HCl. Concomitant use may reduce the analgesic effect and/or precipitate withdrawal symptoms.
Monoamine oxidase inhibitors (MAOIs)	Major	MAOIs have been reported to intensify the effects of opioids causing anxiety, confusion, and significant depression of respiration, or coma. The use of this agent is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
CYP3A4 inducers	Major	Coadministration may significantly decrease plasma oxycodone HCl concentrations. Induction of CYP 3A4 activity by agents such as rifampin, carbamazepine, and phenytoin, may lead to a lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone HCl. If coadministration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate at frequent intervals and consider dose adjustments until stable drug effects are achieved.
CYP 3A4 inhibitors	Major	Coadministration may significantly increase plasma oxycodone HCl concentrations. Inhibition of CYP 3A4 activity by agents such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole, voriconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP 3A4 inhibitors. Evaluate at frequent intervals and consider dose adjustments until stable drug effects are achieved.

CYP 2D6 inhibitors	Moderate	Oxycodone HCl is metabolized in part to oxymorphone via the CYP450 isoenzyme CYP 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine, and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. However, clinicians should be aware of this possible interaction and monitor closely.
Anticholinergics	Major	An increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus, may result from concurrent use with anticholinergics or other medications with anticholinergic activity.
Fluvoxamine	Major	Concurrent use may result in an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus and mental status changes).
Escitalopram	Major	Concurrent use may result in an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus and mental status changes).
Sertraline	Major	Concurrent use of sertraline and oxycodone HCl may result in an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus and mental status changes).
Abiraterone	Major	Concurrent use of abiraterone and oxycodone HCl may result in increased oxycodone HCl plasma concentrations.
Nefazodone	Major	Concurrent use may result in increased oxycodone HCl plasma concentrations and decreased oxycodone HCl clearance.
Cobicistat	Major	Concurrent use of cobicistat and oxycodone may result in increased oxycodone HCl plasma concentrations.
Amiodarone	Major	Concurrent use may result in increased oxycodone HCl plasma concentrations.
Aprepitant	Major	Concurrent use may result in increased oxycodone HCl plasma concentrations and decreased oxycodone HCl clearance.
Meclizine	Major	May result in increased risk of paralytic ileus and increased risk of respiratory and CNS depression.
Carbamazepine	Moderate	Concurrent use may result in decreased oxycodone HCl exposure and plasma concentrations.
Phenytoin	Moderate	Concurrent use may result in decreased oxycodone HCl exposure and plasma concentrations.
Diuretics (e.g., furosemide, hydrochlorothiazide, spironolactone, etc.)	Moderate	Concurrent use may result in decreased diuretic efficacy.
St John's Wort	Moderate	Concurrent use may result in decreased plasma levels and efficacy of oxycodone HCl.
Rifampin	Moderate	Concurrent use may result in decreased oxycodone HCl exposure and plasma concentrations.
Ginseng	Moderate	Concurrent use may result in reduced opioid analgesic effectiveness.
Kava	Moderate	Concurrent use may result in increased central nervous system depression.

*Severity rating per Micromedex

Patient Monitoring Guidelines[1,2]

Assess each patient's risk for opioid addiction, abuse, or misuse prior to initiating therapy and monitor all patients for the development of these behaviors or conditions. “Drug seeking” behaviors should also be monitored to help identify these potential concerns.

Continually re-evaluate patients to assess the maintenance of pain control and the development of adverse reactions. 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. During chronic therapy, periodically reassess the continued need for opioid analgesics. Patients should be closely monitoring when transitioning to Oxaydo® (oxycodone HCl) from another opioid analgesic or from Oxaydo® (oxycodone HCl) to another opioid analgesic as there may be significant inter-patient variability in the relative potency of opioid therapies.

Continuously monitor patients for new or worsening adverse events or changes in medication efficacy, particularly with changes in drug doses and/or frequency. Closely monitor patients when there is the addition or elimination of other agents that may alter the efficacy or adverse event profile of the interacting agent(s). Individuals with renal and/or hepatic impairment as well as the elderly should have initial doses adjusted to account for impaired ability to metabolize and eliminate oxycodone and its metabolites. These individuals should be closely monitored as there is the increased risk of adverse events, particularly with changes in the underlying disease impairment and/or dose adjustments.

The following signs and symptoms should be monitored during therapy with opioids:

- respiratory depression and sedation; following treatment initiation and after dose increases; and particularly in high risk patient (elderly, cachectic, and debilitated patients and those with preexisting respiratory depression or otherwise significantly reduced respiratory reserve)
- exacerbation of biliary tract disease, including acute pancreatitis, in patients with a medical history of these disorders
- hypotension; in ambulatory patients; on initiation and with dose titration; especially when ability to maintain blood pressure is compromised
- worsened seizure control; in patients with a history of seizure disorders
- CNS depression

References

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