HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OXAYDO™ (oxycodone HCl, USP) Tablets for oral use only – CII
Initial U.S. Approval: 1982

----------INDICATIONS AND USAGE----------

- OXAYDO (oxycodone HCl) is an opioid agonist indicated for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate. (1)

----------DOSAGE AND ADMINISTRATION----------

- Opioid naïve - start dosing with 5 to 15 mg every 4 to 6 hours as needed for pain. (2.2)
- Take each tablet, with enough water to ensure complete swallowing immediately after placing in the mouth. (2, 17)
- Must be swallowed whole and is not amenable to crushing and dissolution. Do not use OXAYDO for administration via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes. (2, 17)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 5 mg and 7.5 mg (oxycodone HCl) (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to oxycodone, oxycodone salts, any components of the product, or in any situation where opioids are contraindicated (4)
- Respiratory depression (4)
- Paralytic ileus (4)
- Acute or severe bronchial asthma or hypercarbia (4)

----------WARNINGS AND PRECAUTIONS----------

- Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.1)
- Controlled substance: Oxycodone HCl is a Schedule II controlled substance with an abuse liability similar to other opioids. (5.2)
- CNS effects: Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.3)
- Elevation of intracranial pressure: May be markedly exaggerated in the presence of head injury, or other intracranial lesions. (5.4)
- Hypotensive effect: Increased risk with compromised ability to maintain blood pressure. (5.5)
- Prolonged gastric obstruction: In patients with gastrointestinal obstruction, especially paralytic ileus. (5.6)
- Sphincter of Oddi spasm and diminished biliary/pancreatic secretions. Increased risk with biliary tract disease. (5.7)
- 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, or in elderly or debilitated patients. (5.8)
- Impaired mental/physical abilities: Must use caution with potentially hazardous activities. (5.9)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.10)

----------ADVERSE REACTIONS----------

The most common adverse reactions are nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Acura Pharmaceuticals, Inc. at 1-855-228-7201 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CNS Depressants: Increased risk of respiratory depression, hypotension, profound sedation, or coma. Possible additive central nervous system depression with central nervous system depressants. (7.1)
- Muscle relaxants: Enhances the neuromuscular blocking action of skeletal muscle relaxants and produces an increased degree of respiratory depression. (7.2)
- Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine): May reduce the analgesic effects and/or may precipitate withdrawal symptoms. (7.3)
- Monoamine Oxidase Inhibitors (MAOIs): Use not recommended with or within 14 days of stopping MAOIs. (7.4)
- The CYP3A4 enzyme plays a major role in the metabolism of oxycodone: drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. (7.5)
- Anticholinergics: Increased risk for urinary retention and severe constipation. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Geriatric patients: Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for adverse reactions. (8.5)
- Patients with hepatic impairment (8.6) or renal impairment (8.7): Dose initiation should follow a conservative approach, monitor patients closely and adjust the dose based on clinical response.
- Use in pregnancy only if potential benefit justifies the risk to the fetus (8.1). Women in labor (8.2) and nursing mothers (8.3) should not use OXAYDO.
- Safety and effectiveness in pediatric patients (< 18 years) have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Individualization of Dose
2.2 Initiation of Therapy
2.3 Conversion to OXAYDO
2.4 Maintenance of Therapy
2.5 Cessation of Therapy
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Respiratory Depression
5.2 Misuse and Abuse of Opioids
5.3 Central Nervous System Depressants
5.4 Head Injury and Increased Intracranial Pressure
5.5 Hypotensive Effect
5.6 Gastrointestinal Effects
5.7 Use in Pancreatic/Biliary Tract Disease
5.8 Special Risk Groups
5.9 Driving and Operating Machinery
5.10 Cytochrome P450 3A4 Inhibitors and Inducers
6 ADVERSE REACTIONS
6.1 Clinical Studies
7 DRUG INTERACTIONS
7.1 Central Nervous System Depressants
7.2 Muscle Relaxants
7.3 Mixed Agonist/Antagonist Opioid Analgesics
7.4 Monoamine Oxidase Inhibitors (MAOIs)
7.5 Agents Affecting Cytochrome P450 Enzymes
7.6 Anticholinergics
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
10.1 Signs and Symptoms
10.2 Treatment
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OXAYDO is an immediate-release oral formulation of oxycodone HCl indicated for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate.

2 DOSAGE AND ADMINISTRATION

Selection of patients for treatment with OXAYDO should be governed by the same principles that apply to the use of other potent opioid analgesics. Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension. Healthcare providers should individualize treatment in every case, using non-opioid analgesics, opioids and/or combination products when necessary, and chronic opioid therapy with drugs such as OXAYDO in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and the American Pain Society.

OXAYDO must be swallowed whole. Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see* PATIENT COUNSELING INFORMATION (17)*]*. OXAYDO is not amenable to crushing and dissolution. Do not administer OXAYDO via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes.

2.1 Individualization of Dose

The dose of OXAYDO should be individually adjusted according to severity of pain, and the patient's response, weight, age, and prior analgesic treatment experience. Although it is not possible to list every condition that is important to the selection of the initial dose of OXAYDO, attention must be given to:

1. the daily dose, potency and characteristics of a pure agonist or mixed agonist/antagonist the patient has been taking previously
2. the reliability of the relative potency estimate to calculate the dose of oxycodone HCl needed
3. the degree of opioid tolerance
4. the general condition and medical status of the patient
5. the balance between pain management and adverse reactions
6. the type and severity of the patient's pain
7. risk factors for abuse or addiction, including a prior history of abuse or addiction

2.2 Initiation of Therapy

Patients who have not been receiving opioid analgesics should be started on OXAYDO in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain. The dose should be titrated based upon the individual patient's response to their initial dose of OXAYDO.

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.

Hepatic Impairment

Since oxycodone 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. Dosages should be adjusted according to the clinical situation *[see* USE IN SPECIFIC POPULATIONS (8.6)*]*.

Renal Impairment

Published data reported that elimination of oxycodone 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. Dosages should be adjusted according to the clinical situation *[see* USE IN SPECIFIC POPULATIONS (8.7)*]*.

2.3 Conversion to OXAYDO

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

When converting patients from fixed-ratio opioid/non-opioid drug regimens to OXAYDO, determine whether or not to continue the non-opioid analgesic. Titrate the dose of OXAYDO 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

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

In converting patients from other opioids to OXAYDO, close observation and adjustment of dosage based upon the patient's response to OXAYDO is imperative.

2.4 Maintenance of Therapy

Continual re-evaluation of the patient receiving OXAYDO 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, effort 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.

2.5 Cessation of Therapy

When a patient no longer requires therapy with OXAYDO after chronic use, it is important that therapy be gradually tapered 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 *[see* DRUG ABUSE AND DEPENDENCE (9.3) *for a description of the 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. It is not known at what dose of OXAYDO that treatment may be discontinued without risk of the opioid abstinence syndrome occurring.

3 DOSAGE FORMS AND STRENGTHS

OXAYDO is supplied as white, debossed tablets in two strengths, 5 mg and 7.5 mg of oxycodone HCl, USP, as noted below.

Strength	Description
5 mg	Round, convex, white tablet, debossed “5” on one side, Letter “O” on other side.
7.5 mg	Round, convex, white tablet, debossed “7.5” on one side, Letter “O” on other side.

4 CONTRAINDICATIONS

OXAYDO is contraindicated in patients with respiratory depression in unmonitored settings and in the absence of resuscitative equipment.

OXAYDO is contraindicated in any patient who has or is suspected of having paralytic ileus.

OXAYDO is contraindicated in patients with acute or severe bronchial asthma or hypercarbia.

OXAYDO is contraindicated in patients with known hypersensitivity to oxycodone, oxycodone salts, or any components of the product.

5 WARNINGS AND PRECAUTIONS

5.1 Respiratory Depression

Respiratory depression is the primary risk of OXAYDO. Respiratory depression 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).

OXAYDO must be used 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. In such patients, even usual therapeutic doses of OXAYDO may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids must be employed only under careful medical supervision at the lowest effective dose.

5.2 Misuse and Abuse of Opioids

OXAYDO contains oxycodone HCl, an opioid agonist and a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders.

OXAYDO can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone HCl in situations where the physician or pharmacist is concerned about an increased risk of misuse or abuse.

OXAYDO may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death *[see* DRUG ABUSE AND DEPENDENCE (9)*]*.

Concerns about abuse and addiction should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or misuse of this product.

5.3 Central Nervous System Depressants

Patients receiving narcotic analgesics, general anesthetics, phenothiazines, benzodiazepines, other tranquilizers, sedative-hypnotics, or other central nervous system depressants concomitantly with OXAYDO may exhibit an additive central nervous system depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual dosage of OXAYDO. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Patients should not consume alcoholic beverages, or any medications containing alcohol while taking OXAYDO.

5.4 Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of OXAYDO and its potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, OXAYDO can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

5.5 Hypotensive Effect

OXAYDO 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. OXAYDO may produce orthostatic hypotension in ambulatory patients. OXAYDO must be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.6 Gastrointestinal Effects

Do not administer OXAYDO to patients with gastrointestinal obstruction, especially paralytic ileus because oxycodone HCl diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction.

The administration of OXAYDO may obscure the diagnosis or clinical course in patients with acute abdominal condition.

5.7 Use in Pancreatic/Biliary Tract Disease

Use OXAYDO 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.

5.8 Special Risk Groups

Use OXAYDO 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 *[see* USE IN SPECIFIC POPULATIONS (8)*]*.

Exercise caution in the administration of OXAYDO 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 OXAYDO out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

5.9 Driving and Operating Machinery

OXAYDO 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. The patient using OXAYDO must be cautioned accordingly *[see* DRUG INTERACTIONS (7)*]*.

5.10 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations. The expected clinical results with CYP3A4 inhibitors would be an increase in oxycodone plasma concentrations and possibly increased or prolonged opioid effects. The expected clinical results with CYP3A4 inducers would be a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone.

If co-administration is necessary, caution is advised when initiating oxycodone treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see* DRUG INTERACTIONS (7.5) *and* CLINICAL PHARMACOLOGY (12.3)*]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in 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 clinical practice.

Serious adverse reactions that may be associated with OXAYDO include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock *[see* WARNINGS AND PRECAUTIONS (5) *and* OVERDOSAGE (10)*]*.

The common adverse reactions seen on initiation of therapy with OXAYDO are dose-dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid therapy. The most frequent of the adverse reactions include nausea, constipation, vomiting, headache, and pruritus.

The frequency of adverse reactions during initiation of opioid therapy may be minimized by careful individualization of starting dosage, slow titration and the avoidance of large rapid swings in plasma concentration of the opioid. Many of these adverse reactions will abate as therapy is continued and some degree of tolerance is developed, but others may be expected to remain throughout therapy.

In all patients for whom dosing information was available (n=191) from open-label and double-blind studies involving oxycodone, the following adverse reactions were recorded in oxycodone-treated patients with an incidence of ≥3%. In descending order of frequency they were: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.

The following adverse reactions occurred in less than 3% of patients involved in clinical trials with oxycodone:

Body as a Whole: abdominal pain, accidental injury, allergic reaction, back pain, chills and fever, fever, flu syndrome, infection, neck pain, pain, photosensitivity reaction, and sepsis.

Cardiovascular: deep vein thrombophlebitis, heart failure, hemorrhage, hypotension, migraine, palpitation, and tachycardia.

Digestive: anorexia, diarrhea, dyspepsia, dysphagia, gingivitis, glossitis, and nausea and vomiting.

Hematopoietic and Lymphatic: anemia and leukopenia.

Metabolism and Nutrition: edema, gout, hyperglycemia, iron deficiency anemia, and peripheral edema.

Musculoskeletal: arthralgia, arthritis, bone pain, myalgia, and pathological fracture.

Nervous System: agitation, anxiety, confusion, dry mouth, hypertonia, hypesthesia, nervousness, neuralgia, personality disorder, tremor, and vasodilation.

Respiratory: bronchitis, cough increased, dyspnea, epistaxis, laryngismus, lung disorder, pharyngitis, rhinitis, and sinusitis.

Skin and Appendages: herpes simplex, rash, sweating, and urticaria.

Special Senses: amblyopia.

Urogenital: urinary tract infection.

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

Other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol increase the risk of respiratory depression, hypotension, profound sedation, or coma. Use OXAYDO with caution and in reduced dosages in patients taking these agents.

Patients should not consume alcoholic beverages, or any medications containing alcohol while taking OXAYDO.

7.2 Muscle Relaxants

OXAYDO may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

7.3 Mixed Agonist/Antagonist Opioid Analgesics

Do not administer mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone HCl. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone HCl and/or may precipitate withdrawal symptoms.

7.4 Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion, and significant depression of respiration or coma. The use of OXAYDO is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

7.5 Agents Affecting Cytochrome P450 Enzymes

CYP3A4 Inhibitors

A published study showed that the co-administration with voriconazole, a CYP3A4 inhibitor, significantly increased the plasma concentrations of oxycodone. Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), 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 CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[*see CLINICAL PHARMACOLOGY (12.3)*]*.

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, significantly decreased plasma oxycodone concentrations. Induction of CYP3A4 activity by its inducers, 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. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see* CLINICAL PHARMACOLOGY (12.3)*]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6. 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.

7.6 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B: There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. Animal reproduction studies have not revealed evidence of teratogenicity or fetal harm. Because animal reproduction studies are not always predictive of human response, OXAYDO should be used during pregnancy only if clearly needed.

Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg and 25 mg/kg (approximately 2 and 5 times the daily oral dose of 90 mg on a mg/m^2 basis) respectively, it was not teratogenic or embryo-fetal toxic.

Non-teratogenic Effects

Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. OXAYDO is not recommended for use in women during or immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. Neonates, whose mothers received opioid analgesics during labor, must be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, must be available for reversal of narcotic-induced respiratory depression in the neonate.

8.3 Nursing Mothers

Low levels of oxycodone have been detected in maternal milk. The amount of oxycodone 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. There is potential for serious adverse reactions in nursing infants from oxycodone that includes respiratory depression, sedation and potentially withdrawal symptoms when the mother stops taking oxycodone HCl. As such, one should consider either discontinuing nursing or discontinuing the drug, while taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety, effectiveness, and pharmacokinetics of OXAYDO in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to OXAYDO. 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.

8.6 Hepatic Impairment

Since oxycodone is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Follow a conservative approach to initiate dosing in patients with hepatic impairment. Monitor patients closely and adjust the dose based on clinical response *[see* DOSAGE AND ADMINISTRATION (2.2)*]*.

8.7 Renal Impairment

Information from oxycodone HCl indicates that patients with renal impairment (defined as a creatinine clearance <60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function. Use a conservative approach to initiate dosing in patients with renal impairment. Monitor patients closely and adjust the dose based on clinical response *[see* DOSAGE AND ADMINISTRATION (2.2)*]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OXAYDO contains oxycodone HCl, a mu-agonist opioid of the morphine type and a Schedule II controlled substance. OXAYDO, like other opioids used in analgesia, can be abused and is subject to criminal diversion.

9.2 Abuse

Abuse of OXAYDO poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol or other substances.

“Drug-seeking” behavior is very common in persons with substance abuse 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” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. The converse is also true. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by intentional non-therapeutic use of a drug for its rewarding psychological or physiological effects, often in combination with other psychoactive substances. Misuse includes use of a drug in ways other than prescribed or directed by a healthcare provider. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

OXAYDO is intended for oral use only. Abuse of OXAYDO poses a risk of overdose and death. The risk of overdose and death is increased with concurrent abuse of alcohol or other central nervous system depressants. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

In a double-blind, active-comparator, crossover study in 40 non-dependent recreational opioid users, "drug liking" responses and single-dose safety of crushed OXAYDO tablets were compared with crushed immediate-release Oxycodone tablets when subjects self-administered the drug intranasally. The presence of sequence effects resulted in questionable reliability of the second period data. First period data demonstrated small numeric differences in the median and mean drug liking scores, lower in response to OXAYDO than immediate-release oxycodone. Thirty percent of subjects exposed to OXAYDO responded that they would not take the drug again compared to 5% of subjects exposed to immediate-release oxycodone. Study subjects self-administering OXAYDO reported a higher incidence of nasopharyngeal and facial adverse events and a decreased ability to completely insufflate two crushed tablets within a fixed time period (21 of 40 subjects). 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 no evidence that OXAYDO has a reduced abuse liability compared to immediate-release oxycodone.

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.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms.

9.3 Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. In general, opioids should not be abruptly discontinued.

10 OVERDOSAGE

10.1 Signs and Symptoms

Acute overdose with OXAYDO can be manifested by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle

flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, cardiac arrest and death.

Oxycodone HCl may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

10.2 Treatment

To treat OXAYDO overdose, primary attention must be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) must be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonist naloxone is a specific antidote to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to OXAYDO overdose**.** If needed, the appropriate dose of naloxone HCl should be administered simultaneously with efforts at respiratory resuscitation (see prescribing information for naloxone HCl for the details).

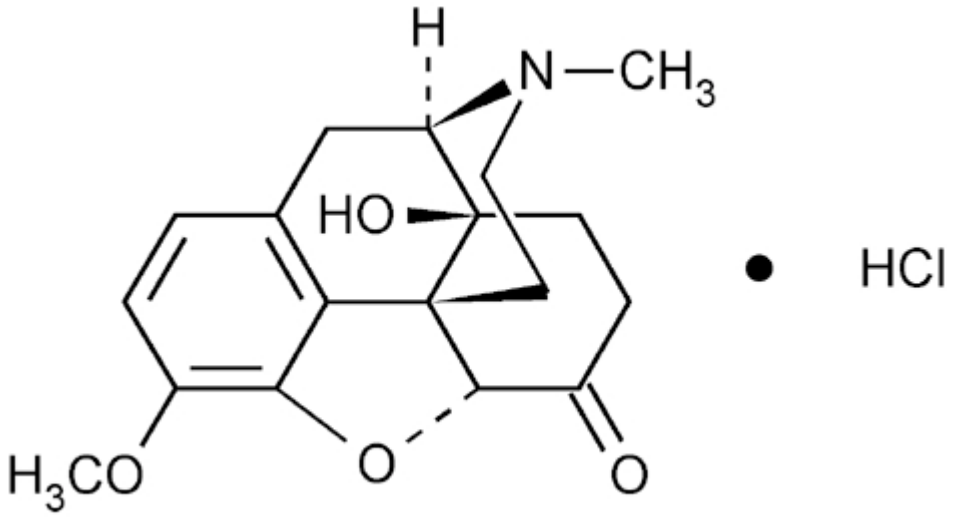
Since the duration of action of OXAYDO is expected to exceed that of the antagonist, the patient must be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. Opioid antagonists must be administered cautiously to persons who are suspected to be physically dependent on any opioid agonist, including oxycodone (see Opioid-Tolerant Individuals).

Opioid-Tolerant Individuals: In an individual physically dependent on opioids, administration of a usual dose of antagonist will precipitate an acute withdrawal. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Reserve use of an opioid antagonist for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, initiate administration of the antagonist with care and by titration with smaller than usual doses.

11 DESCRIPTION

OXAYDO (oxycodone HCl, USP) tablets are an immediate-release opioid analgesic intended for oral administration only. OXAYDO contains oxycodone HCl, USP as the active analgesic ingredient. The tablets are round, convex, white and debossed with the strength (5 or 7.5) on one side and the letter “O” on the other side. OXAYDO also contain colloidal silicon dioxide NF; crospovidone NF; magnesium stearate NF; microcrystalline cellulose NF; polyethylene oxide NF; and sodium lauryl sulfate NF.

Chemically, oxycodone HCl is 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one HCl, a white, odorless crystalline powder. Oxycodone HCl is soluble in water (1 g in 6 to 7 mL). The molecular weight of oxycodone HCl is 351.82. The molecular formula for oxycodone HCl is $C_{18}H_{21}NO_4$•HCl, and the structure is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone HCl is a pure opioid agonist and is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all pure opioid agonists, there is no ceiling effect to analgesia.

12.2 Pharmacodynamics

The relationship between the plasma level of oxycodone and the analgesic response will depend on the patient's age, state of health, medical condition, and extent of previous opioid treatment.

The minimum effective plasma concentration of oxycodone to achieve analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. Thus, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time with repeated dosing due to an increase in pain and/or development of tolerance.

Effects on Central Nervous System

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

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. 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

Gastric, biliary, and pancreatic secretions are decreased by oxycodone HCl. Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone located in the medulla. The frequency and severity of emesis gradually diminishes with time.

Oxycodone may cause a decrease in the secretion of hydrochloric acid in the stomach that reduces motility while increasing the tone of 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, in therapeutic doses, produces peripheral vasodilation (arterial and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Caution must be used in hypovolemic patients, such as those suffering acute myocardial infarction, because oxycodone may cause or further aggravate their hypotension. Caution must also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats, and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to hormonal changes that may manifest as symptoms of hypogonadism.

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.

12.3 Pharmacokinetics

The analgesic activity of OXAYDO is primarily due to the parent drug oxycodone.

The pharmacokinetics of oxycodone after OXAYDO administration are characterized by peak plasma concentrations occurring on average within 1.2 to 1.4 hours of the first dose under fasted conditions. Thereafter, oxycodone concentrations fall with an average terminal half-life ranging between 3-4 hours. OXAYDO is bioequivalent with Oxycodone immediate-release tablets in the fasted state, with no differences identified in the time to peak exposure (T_{max}) and terminal elimination half-life ($T_{½}$) of oxycodone between administration of OXAYDO and Oxycodone immediate-release tablets. Dose proportionality was established for OXAYDO at doses of 5 mg, 10 mg, and 15 mg (oxycodone HCl) based on proportional increases in oxycodone C_{max} and AUC exposure levels.

Food Effect

When administered with a high fat meal, mean AUC values are increased by 21% and peak concentrations are decreased by 14%. Food causes a delay in T_{max} from 1.25 to 3.00 hours. These changes in oxycodone pharmacokinetics are not considered clinically relevant; therefore, OXAYDO can be taken without regard to food.

Absorption

The oral bioavailability of oxycodone is 60% to 87%. The high oral bioavailability of oxycodone (compared to other oral opioids) is due to lower pre-systemic and/or first-pass metabolism of oxycodone compared to other oral opioids.

Distribution

Following intravenous administration, the volume of distribution for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was approximately 45%. Oxycodone has been found in breast milk *[see* USE IN SPECIFIC POPULATIONS (8.3)*]*.

Metabolism

Oxycodone HCl is extensively metabolized by multiple metabolic pathways to noroxycodone, oxymorphone, and noroxymorphone, which are subsequently glucuronidated. CYP3A4 mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with less contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be 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 was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

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%; 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/min for adults. Apparent elimination half-life of oxycodone following the administration of oxycodone was 3.5 to 4 hours.

Special Populations

Elderly: Information obtained from oxycodone indicate that the plasma concentrations of oxycodone did not appear to be increased in patients over the age of 65.

Gender: Information obtained from oxycodone support the lack of gender effect on the pharmacokinetics of oxycodone.

Renal Insufficiency: Information obtained from oxycodone indicate that patients with renal impairment (defined as creatinine clearance <60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function *[see* DOSAGE AND ADMINISTRATION (2.2)*]*.

Hepatic Failure: Since oxycodone is extensively metabolized, its clearance may decrease in patients with hepatic impairment *[see* DOSAGE AND ADMINISTRATION (2.2)*]*.

Drug-Drug Interactions

CYP3A4 Inhibitors

CYP3A4 is the major enzyme involved in noroxycodone formation. A published study showed that the coadministration of voriconazole, a CYP3A4 inhibitor, increased oxycodone AUC and Cmax by 3.6 and 1.7 fold, respectively *[see* WARNINGS AND PRECAUTIONS (5.10) *and* DRUG INTERACTIONS (7.5)*]*.

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and Cmax values by 86% and 63%, respectively *[see* WARNINGS AND PRECAUTIONS (5.10) *and* DRUG INTERACTIONS (7.5)*]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Studies of oxycodone HCl to evaluate its carcinogenic potential have not been conducted.

Mutagenesis

Oxycodone HCl was genotoxic in an *in vitro* mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) and in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).

Impairment of Fertility

The potential effects of oxycodone on male and female fertility have not been evaluated.

16 HOW SUPPLIED/STORAGE AND HANDLING

OXAYDO (oxycodone HCl, USP) is supplied as round, convex, white tablets as follows:

5 mg tablets debossed with the strength “5” on one side and the letter “O” on the other side.

NDC 48964-525-01 Bottles of 100 tablets

7.5 mg tablets debossed with the strength “7.5” on one side and the letter “O” on the other side.

NDC 48964-526-01 Bottles of 100 tablets

Dispense in tight container as defined in the USP, with a child-resistant closure.

Store at 25ºC (77ºF); with excursions permitted to 15º-30ºC (59º-86ºF) [See USP Controlled Room Temperature].

Protect from moisture.

Handling

All opioids, including OXAYDO, are liable to diversion and misuse both by the general public and healthcare workers and must be handled accordingly.

DEA Schedule II Order Form Required

Prescribing Information as of December 2014

Distributed by Acura Pharmaceuticals, Inc., Palatine, IL 60067

17 PATIENT COUNSELING INFORMATION

Provide the following information to patients receiving OXAYDO or their caregivers:

- Advise patients that OXAYDO is a narcotic pain reliever and must be taken only as directed.
- Advise patients to take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth. Advise patients that OXAYDO tablets must be swallowed whole. Do not crush or dissolve. Do not use OXAYDO for administration via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes.

- Advise patients not to pre-soak, lick or otherwise wet the tablet prior to placing in the mouth.
- Advise patients to take OXAYDO only as directed.
- Advise patients not to adjust the dose of OXAYDO without consulting with a physician or other healthcare professional.
- Advise patients that OXAYDO may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery). Advise patients started on OXAYDO or patients whose dose has been adjusted to refrain from any potentially dangerous activity until it is established that they are not adversely affected.
- Instruct patients not to combine OXAYDO with central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, and not to combine with alcohol because dangerous additive effects may occur, resulting in serious injury or death.
- Instruct women of childbearing potential who become or are planning to become pregnant to consult a physician prior to initiating or continuing therapy with OXAYDO. Advise patients that safe use in pregnancy has not been established and that prolonged use of opioid analgesics, including OXAYDO, during pregnancy may cause fetal-neonatal physical dependence, and neonatal withdrawal may occur.
- If patients have been receiving treatment with OXAYDO for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide a dose schedule to help patients gradually discontinue the medication.
- Advise patients that sharing this OXAYDO can result in fatal overdose and death.
- Advise patients that OXAYDO is a potential drug of abuse. They must protect it from theft. Patients should keep OXAYDO in a locked cabinet, drawer, or medicine safe. It must never be given to anyone other than the individual for whom it was prescribed.
- Instruct patients to keep OXAYDO in a secure place out of the reach of children. When OXAYDO is no longer needed, the unused tablets should be destroyed by flushing them down the toilet.
- Advise patients taking OXAYDO of the potential for severe constipation; appropriate laxatives and/or stool softeners as well as other appropriate treatments should be initiated from the onset of opioid therapy.
- Advise patients of the most common adverse reactions that may occur while taking OXAYDO: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.
- Advise patients to call 911 or the local Poison Control center and get emergency help immediately if they take more OXAYDO than prescribed.
- Advise patients that if they miss a dose to take it as soon as possible. If it is almost time for the next dose, skip the missed dose and take the next dose at the regularly scheduled time. Do not take 2 doses at once unless instructed by their healthcare provider. If they are not sure about their dosing, call their healthcare provider.

Rx Only

Distributed by:

Acura Pharmaceuticals, Inc. Palatine, Illinois 60067

Revised: 12/2014