OXYCODONE AND ASPIRIN- oxycodone and aspirin tablet
Epic Pharma, LLC

Oxycodone and Aspirin Tablets CII

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF OXYCODONE AND ASPIRIN TABLETS

Addiction, Abuse, and Misuse

Because the use of oxycodone and aspirin tablets exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions (see WARNINGS).

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of oxycodone and aspirin tablets, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of oxycodone and aspirin tablets are essential (see WARNINGS).

Accidental Ingestion

Accidental ingestion of even one dose of oxycodone and aspirin tablets, especially by children, can result in a fatal overdose of oxycodone (see WARNINGS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of oxycodone and aspirin tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate [*see WARNINGS*].

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery [*see WARNINGS*].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription [*see WARNINGS*].

Cytochrome P450 3A4 Interaction

The concomitant use of oxycodone and aspirin tablets with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4

inducer may result in an increase in oxycodone plasma concentration. Regularly evaluate patients receiving oxycodone and aspirin tablets and any CYP3A4 inhibitor or inducer frequently (see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions).

DESCRIPTION

Oxycodone and Aspirin Tablets are an immediate-release opioid agonist intended for oral administration only.

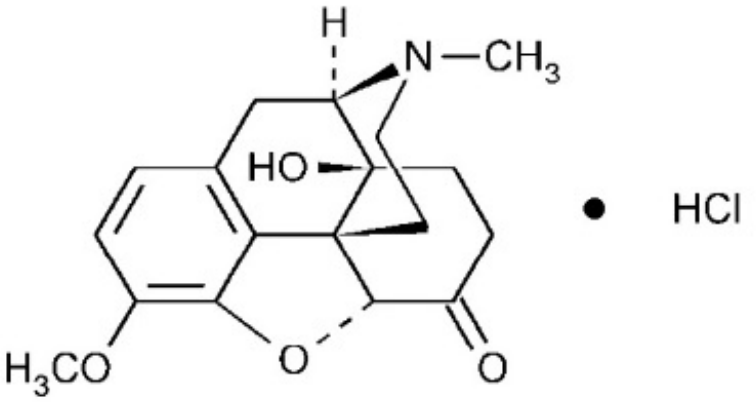
Each Oxycodone and Aspirin Tablet contains:

Oxycodone Hydrochloride, USP 4.8355 mg*

Aspirin, USP 325 mg

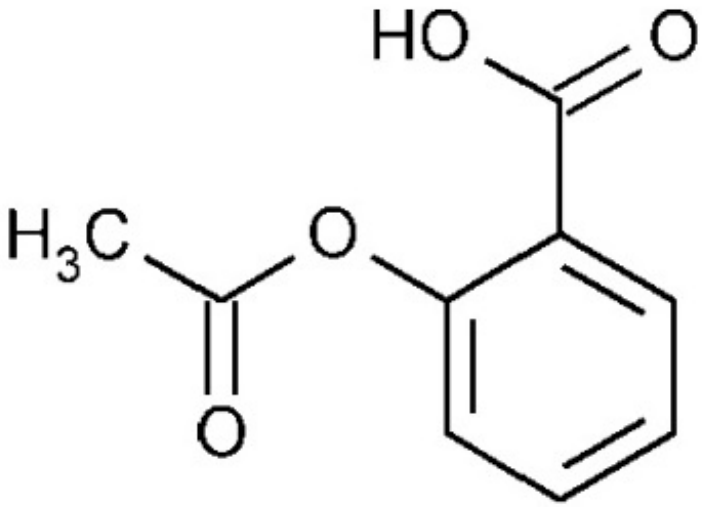
*4.8355 mg oxycodone HCl is equivalent to 4.3346 mg of oxycodone as the free base.

Oxycodone and Aspirin Tablets USP also contain the following inactive ingredients: microcrystalline cellulose, starch and zinc stearate.



$C_{18}N_{21}NO_4$ •HCl MW 351.82

The oxycodone hydrochloride component is Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5α)-, a white to off-white, hygroscopic crystals or powder, odorless, soluble in water; slightly soluble in alcohol and is represented by the following structural formula:



$C_9H_8O_4$ MW 180.16

CLINICAL PHARMACOLOGY

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 of oxycodone 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.

Aspirin (acetylsalicylic acid) works by inhibiting the body’s production of prostaglandins, including prostaglandins involved in inflammation. Prostaglandins cause pain sensations by stimulating muscle contractions and dilating blood vessels throughout the body. In the CNS, aspirin works on the hypothalamus heat-regulating center to reduce fever, however, other mechanisms may be involved.

Pharmacodynamics

Effects on the 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 increases in both 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 the 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.

Aspirin can produce gastrointestinal injury (lesions, ulcers) through a mechanism that is not yet completely understood, but may involve a reduction in eicosanoid synthesis by the gastric mucosa. Decreased production of prostaglandins may compromise the defenses of the gastric mucosa and the activity of substances involved in tissue repair and ulcer healing.

Effects on the Cardiovascular System

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

Use caution 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.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans (see ADVERSE REACTIONS). They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time 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).

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 opioid agonists. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance (see DOSAGE AND ADMINISTRATION).

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).

The dose of oxycodone and aspirin tablets must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients (see DOSAGE AND ADMINISTRATION).

Platelet Aggregation

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A2. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin 12 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

Pharmacokinetics

Absorption

The mean absolute oral bioavailability of oxycodone in cancer patients was reported to be about 87%. This high oral bioavailability is due to low pre-systemic elimination and/or first-pass metabolism.

Distribution

The volume of distribution after intravenous administration is 211.9 ±186.6 L. Oxycodone has been shown to be 45% bound to human plasma proteins *in vitro*. Oxycodone has been found in breast milk (see PRECAUTIONS).

Aspirin is hydrolyzed primarily to salicylic acid in the gut wall and during first-pass metabolism through the liver. Salicylic acid is absorbed rapidly from the stomach, but most of the absorption occurs in the proximal small intestine. Following absorption, salicylate is distributed to most body tissues and fluids, including fetal tissues, breast milk, and the CNS. High concentrations are found in the liver and kidneys. Salicylate is variably bound to serum proteins, particularly albumin.

Elimination

Metabolism

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

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at

opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone, is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant, based on the amount formed. Other metabolites (α-and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

The biotransformation of aspirin occurs primarily in the liver by the microsomal enzyme system. With a plasma half-life of approximately 15 minutes, aspirin is rapidly hydrolyzed to salicylate. At low doses, salicylate elimination follows first-order kinetics. The plasma half-life of salicylate is approximately 2 to 3 hours.

Excretion

Free and conjugated noroxycodone, free and conjugated oxycodone, and oxymorphone are excreted in human urine following a single oral dose of oxycodone. Approximately 8% to 14% of the dose is excreted as free oxycodone over 24 hours after administration.

Approximately 10% of aspirin is excreted as unchanged salicylate in the urine. The major metabolites excreted in the urine are salicyluric acid (75%), salicyl phenolic glucuronide (10%), salicyl acyl glucuronide (5%), and gentisic and gentisuric acid (less than 1%) each. Eighty to 100% of a single dose is excreted in the urine within 24 to 72 hours.

Drug -Drug Interactions (see PRECAUTIONS)

Inhibitors of CYP3A4

Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone and aspirin tablets, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone, which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and Cmax by 3.6 and 1.7 fold, respectively. The expected clinical results would be increased or prolonged opioid effects.

Inducers of CYP450

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63% respectively. The expected clinical results would be lack of efficacy or, possibly, development of abstinence syndrome in a patient who had developed physical dependence to oxycodone. Induction of CYP3A4 may be of greatest importance given oxycodone’s metabolic pathways.

INDICATIONS AND USAGE

Oxycodone and aspirin tablets are indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, which can occur at any dosage or duration (see WARNINGS), reserve oxycodone and aspirin tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics)

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

Oxycodone and Aspirin tablets should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

CONTRAINDICATIONS

Oxycodone and aspirin tablets are contraindicated in patients with:

- Significant respiratory depression (see WARNINGS)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (see WARNINGS)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (see WARNINGS)
- Hypersensitivity to oxycodone or aspirin, (e.g. angioedema) (see WARNINGS)
- Patients with hemophilia.
- Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye syndrome (see WARNINGS)

WARNINGS

Addiction, Abuse, and Misuse

Oxycodone and aspirin tablets contain Oxycodone, a Schedule II controlled substance. As an opioid, oxycodone and aspirin tablets exposes users to the risks of addiction, abuse, and misuse (see DRUG ABUSE AND DEPENDENCE).

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxycodone and aspirin 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 and aspirin tablets, and reassess all patients receiving oxycodone and aspirin 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 and aspirin

tablets but use in such patients necessitates intensive counseling about the risks and proper use of oxycodone and aspirin tablets along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [see WARNINGS, DOSAGE AND ADMINISTRATION].

Opioids are sought by nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing oxycodone and aspirin tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and proper disposal of unused drug (see PRECAUTIONS; Information for Patients/Caregivers). 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.

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). Carbon dioxide (CO_2) 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 and aspirin tablets, the risk is greatest during the initiation of therapy or following a dosage increase.

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

Accidental ingestion of even one dose of oxycodone and aspirin tablets, especially by children can result in respiratory depression and death due to an overdose of oxycodone. Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see PRECAUTIONS; Information for Patients/Caregivers].

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper (see DOSAGE AND ADMINISTRATION).

Patients Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with oxycodone and aspirin tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and

emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered [see PRECAUTIONS; Information for Patients/Caregivers].

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of other CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone [see WARNINGS, PRECAUTIONS; Information for Patients/Caregivers, OVERDOSAGE].

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 and aspirin tablets with benzodiazepines and/or other CNS depressants, including alcohol (e.g., nonbenzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). 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 pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see PRECAUTIONS; Drug Interactions].

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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation).

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see WARNINGS, DOSAGE AND ADMINISTRATION].

Advise both patient and caregivers about the risks of respiratory depression and sedation when oxycodone and aspirin tablets is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse; and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see PRECAUTIONS; Drug Interactions].

Neonatal Opioid Withdrawal Syndrome

Use of oxycodone and aspirin tablets for an extended period of time during pregnancy

can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike 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 accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see PRECAUTIONS; Information for Patients/Caregivers, Pregnancy).

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 do all of the following:

- 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 prescribed. 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 Mediation Guide that they will receive from their pharmacist every time an opioid analgesic is dispended 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 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.

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

Concomitant use of oxycodone and aspirin 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 prolong opioid adverse reactions, which may cause potentially fatal respiratory depression (see WARNINGS), particularly when an inhibitor is added after a stable dose of oxycodone and aspirin tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in oxycodone and aspirin tablets -treated patients may increase oxycodone and aspirin tablets plasma concentrations and prolong opioid adverse reactions. When using oxycodone and aspirin tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in oxycodone and aspirin tablets -treated patients, evaluate patients at frequent intervals and consider

dosage reduction of oxycodone and aspirin tablets until stable drug effects are achieved (see PRECAUTIONS; Drug Interactions).

Concomitant use of oxycodone and aspirin 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 and aspirin tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, evaluate patients at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur (see PRECAUTIONS; Drug Interactions).

Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect [see DRUG ABUSE AND DEPENDENCE]. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Through the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) [see WARNINGS, DOSAGE AND ADMINISTRATION].

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

The use of oxycodone and aspirin 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 and aspirin tablets -treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, 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 and aspirin tablets (see WARNINGS).

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).

Regularly evaluate patients, particularly when initiating and titrating oxycodone and aspirin tablets and when oxycodone and aspirin tablets is given concomitantly with other drugs that depress respiration (see WARNINGS). Alternatively, consider the use of non-

opioid analgesics in these patients.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than 1 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. Wean the patient off of the opioid to allow 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.

Severe Hypotension

Oxycodone and aspirin tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics). Regularly evaluate these patients for signs of hypotension after initiating or titrating the dosage of oxycodone and aspirin tablets. In patients with circulatory shock, oxycodone and aspirin tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of oxycodone and aspirin tablets in patients with circulatory shock.

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 CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), oxycodone and aspirin tablets may reduce 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 and aspirin tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of oxycodone and aspirin tablets in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions

Oxycodone and aspirin tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

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

Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in oxycodone and aspirin tablets may increase the frequency of seizures

in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during oxycodone and aspirin tablets therapy.

Withdrawal

Do not abruptly discontinue oxycodone and aspirin tablets in a patient physically dependent on opioids. When discontinuing oxycodone and aspirin tablets, in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone and aspirin in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain (see DOSAGE AND ADMINISTRATION, DRUG ABUSE AND DEPENDENCE).

Additionally, avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including oxycodone and aspirin tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. (see PRECAUTIONS; Drug Interactions).

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including oxycodone and aspirin tablets, in pregnant women at about 30 weeks gestation and later. NSAIDs including oxycodone and aspirin tablets, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including oxycodone and aspirin tablets, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit oxycodone and aspirin tablets use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if oxycodone and aspirin tablets treatment extends beyond 48 hours. Discontinue oxycodone and aspirin tablets if oligohydramnios occurs and follow up according to clinical practice [see PRECAUTIONS; Pregnancy].

Risks of Driving and Operating Machinery

Oxycodone and aspirin 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 and aspirin tablets and know how they will react to the medication (see PRECAUTIONS: Information for Patients/Caregivers).

Hypersensitivity to Oxycodone or Aspirin, (e.g. angioedema)

Oxycodone and aspirin tablets are contraindicated in patients with known hypersensitivity to oxycodone or aspirin, and in any situation where opioids or aspirin are contraindicated.

Reye Syndrome

Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye syndrome with concomitant use of aspirin in certain viral illnesses

Serious Skin Reactions

NSAIDs, including aspirin, a component of oxycodone and aspirin tablets, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of oxycodone and aspirin tablets at the first appearance of skin rash or any other sign of hypersensitivity. Oxycodone and aspirin tablets is contraindicated in patients with previous serious skin reactions to NSAIDs [*seeContraindications].*

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs such as oxycodone and aspirin tablets. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue oxycodone and aspirin tablets and evaluate the patient immediately.

Alcohol Warning

Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

Peptic Ulcer Disease

Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

PRECAUTIONS

General

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Hemorrhage

Aspirin may increase the likelihood of hemorrhage due to its effect on the gastric mucosa and platelet function (prolongation of bleeding time). Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

Ambulatory Surgery and Postoperative Use

Oxycodone and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with use of opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Information for Patients/Caregivers

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store oxycodone and aspirin tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving oxycodone and aspirin tablets unsecured can pose a deadly risk to others in the home (see WARNINGS, DRUG ABUSE AND DEPENDENCE).

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused oxycodone and aspirin tablets should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of oxycodone and aspirin tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death (see WARNINGS). Instruct patients not to share oxycodone and aspirin tablets with others and to take steps to protect oxycodone and aspirin tablets from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting oxycodone and aspirin tablets or when the dosage is increased, and that it can occur even at recommended dosages. Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see WARNINGS].

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death (see WARNINGS).

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if oxycodone and aspirin tablets is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider (see WARNINGS, PRECAUTIONS; Drug Interactions).

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with oxycodone and aspirin tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) [see WARNINGS, DOSAGE AND ADMINISTRATION].

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone’s effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered [see OVERDOSAGE].

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including sensitivity to pain, or new pain [see WARNINGS; ADVERSE REACTIONS].

Serotonin Syndrome

Inform patients that oxycodone and aspirin tablets could cause a rare but potentially life-threatening condition called serotonin syndrome resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications.

MAOI Interaction

Inform patients to avoid taking oxycodone and aspirin tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking oxycodone and aspirin tablets (see PRECAUTIONS; Drug Interactions).

Important Administration Instructions

Instruct patients how to properly take oxycodone and aspirin tablets. The usual dosage is one tablet every 6 hours as needed for pain. The maximum daily dose of aspirin should not exceed 4 grams (see DOSAGE AND ADMINISTRATION, PRECAUTIONS)

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue oxycodone and aspirin tablets without first discussing a tapering plan with the prescriber (see DOSAGE AND ADMINISTRATION).

Driving or Operating Heavy Machinery

Inform patients that oxycodone and aspirin tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see WARNINGS].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see ADVERSE REACTIONS, CLINICAL PHARMACOLOGY].

Adrenal Insufficiency

Inform patients that oxycodone and aspirin tablets could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see WARNINGS].

Hypotension

Inform patients that oxycodone and aspirin tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in oxycodone and aspirin tablets. Advise patients how to recognize such a reaction and when to seek medical attention (see CONTRAINDICATIONS, ADVERSE REACTIONS).

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of oxycodone and aspirin tablets for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated (see WARNINGS, PRECAUTIONS; Pregnancy)

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that oxycodone and aspirin tablets can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy. Inform pregnant women to avoid use of aspirin and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with oxycodone and aspirin tablets is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [see WARNINGS; Fetal Toxicity, PRECAUTIONS; Pregnancy].

Lactation

Advise breastfeeding women using oxycodone and aspirin tablets to carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct breastfeeding women to seek immediate medical care if they notice these signs.

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible (see ADVERSE REACTIONS).

Serious Skin Reactions, including DRESS

Advise patients to stop taking oxycodone and aspirin tablets immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [see WARNINGS].

Laboratory Tests

Although oxycodone may cross-react with some drug urine tests, no available studies were found which determined the duration of detectability of oxycodone in urine drug screens. However, based on pharmacokinetic data, the approximate duration of detectability for a single dose of oxycodone is roughly estimated to be one to two days following drug exposure.

Urine testing for opiates may be performed to determine illicit drug use and for medical reasons such as evaluation of patients with altered states of consciousness or monitoring efficacy of drug rehabilitation efforts. The preliminary identification of opiates

in urine involves the use of an immunoassay screening and thin-layer chromatography (TLC). Gas chromatography/mass spectrometry (GC/MS) may be utilized as a third-stage identification step in the medical investigational sequence for opiate testing after immunoassay and TLC. The identities of 6-keto opiates (e.g., oxycodone) can further be differentiated by the analysis of their methoxime-trimethylsilyl (MO-TMS) derivative.

Table 1: Clinically Significant Drug Interactions with Oxycodone and Aspirin Tablets

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of oxycodone and aspirin 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 and aspirin tablets and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of oxycodone and aspirin tablets is achieved (see WARNINGS). After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease (see CLINICAL PHARMACOLOGY), 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 and aspirin tablets until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the oxycodone and aspirin tablets dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal.
Examples	

	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of oxycodone and aspirin tablets and CYP3A4 inducers can decrease the plasma concentration of oxycodone (see CLINICAL PHARMACOLOGY), resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone (see WARNINGS). After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase (see CLINICAL PHARMACOLOGY), which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the oxycodone and aspirin tablets dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal and sedation. If a CYP3A4 inducer is discontinued, consider oxycodone and aspirin tablets dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation.
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, increases the risk of 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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see WARNINGS].
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.
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue oxycodone and aspirin 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 effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol),), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), 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 WARNINGS).
Intervention:	The use of oxycodone and aspirin 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 and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of oxycodone and aspirin tablets and/or 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 and aspirin tablets and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Evaluate 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 use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Evaluate patients for signs of urinary retention or reduced gastric motility when oxycodone and aspirin tablets is used concomitantly with anticholinergic drugs.

Analgesics	
Clinical Impact:	Analgesics may reduce the analgesic effect of oxycodone or may precipitate withdrawal symptoms
Intervention:	Should be administered with caution to a patient who has received or is receiving a full opioid agonist such as oxycodone.
Examples:	Pentazocine, nalbuphine, naltrexone, and butorphanol

Drug/Drug Interactions with Aspirin

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Aspirin may enhance the serious side and toxicity of methotrexate due to displacement from its plasma protein binding sites and/or reduced renal clearance.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAIDs should be avoided because this may increase bleeding or lead to decreased renal function. Aspirin may enhance the serious side effects and toxicity of

ketorolac, due to displacement from its plasma protein binding sites and/or reduced renal clearance.

Oral Hypoglycemics Agents: Aspirin may increase the serum glucose-lowering action of insulin and sulfonylureas leading to hypoglycemia.

Uricosuric Agents: Salicylates antagonize the uricosuric action of probenecid or sulfinpyrazone.

Drug/Laboratory Test Interactions

Depending on the sensitivity/specificity and the test methodology, the individual components of oxycodone and aspirin tablets may cross-react with assays used in the preliminary detection of cocaine (primary urinary metabolite, benzoylecgonine) or marijuana (cannabinoids) in human urine. A more specific alternate chemical method must be used in order to obtain a confirmed analytical result. The preferred confirmatory method is gas chromatography/mass spectrometry (GC/MS). Moreover, clinical considerations and professional judgment should be applied to any drug-of-abuse test result, particularly when preliminary positive results are used.

Salicylates may increase the protein bound iodine (PBI) result by competing for the protein binding sites on pre-albumin and possibly thyroid-binding globulins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of oxycodone and aspirin have not been conducted.

Mutagenesis

The combination of oxycodone and aspirin has not been evaluated for mutagenicity. Oxycodone alone was negative in a bacterial reverse mutation assay (Ames), an *in vitro* chromosome aberration assay with human lymphocytes without metabolic activation and an *in vivo* mouse micronucleus assay. Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation and in the mouse lymphoma assay with or without metabolic activation. Aspirin induced chromosome aberrations in cultured human fibroblasts.

Impairment of Fertility

Animal studies to evaluate the effects of oxycodone on fertility have not been conducted. Aspirin has been shown to inhibit ovulation in rats.

Pregnancy

Risk Summary

Use of opioid analgesics for extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome (see WARNINGS). Available data with oxycodone and aspirin tablets are insufficient to inform a drug-associated risk for major birth defects and miscarriage. Reproduction studies in rats and rabbits demonstrated that oral administration of oxycodone was not teratogenic or embryo-fetal toxic. 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.

Use of NSAIDs, including aspirin, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of oxycodone and aspirin tablets use between about 20 and 30 weeks of gestation, and avoid oxycodone and aspirin tablets use at about 30 weeks of gestation and later in pregnancy *[see* WARNINGS; Fetal Toxicity*]*.

Premature Closure of Fetal Ductus Arteriosus:

Use of NSAIDs, including aspirin, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as aspirin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. 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:
Use of opioid analgesics for extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal withdrawal syndrome shortly after birth.
Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, and manage accordingly (see WARNINGS).

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because

NSAIDs, including oxycodone and aspirin tablets, can cause premature closure of the fetal

ductus arteriosus *[see* WARNINGS; Fetal Toxicity*]*.

Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the

lowest effective dose and shortest duration possible. If oxycodone and aspirin tablets treatment

extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If

oligohydramnios occurs, discontinue oxycodone and aspirin tablets and follow up according to

clinical practice *[see* WARNINGS; Fetal Toxicity*]*.

Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and pyscho-physiologic effects in neonates. An opioid antagonist, such as naloxone must be available for reversal of opioid-induced respiratory depression in the neonate. Oxycodone and aspirin tablets are not recommended for use in women during and immediately prior to labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics, including oxycodone and aspirin 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 dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus: Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment: Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug

exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

Reproduction studies in rats and rabbits demonstrated that oral administration of oxycodone was not teratogenic or embryo-fetal toxic. 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 Postnatal Day 1, 3, and 5; 0.3-times an adult human dose of 60 mg/day, on a mg/m^2 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/m^2 basis).

Lactation

Risk Summary

Available data from lactation studies indicate that oxycodone is present in breastmilk and that doses of less than 60 mg/day of the immediate-release formulation are unlikely to result in clinically relevant exposures in breastfed infants. A pharmacokinetics study utilizing opportunistic sampling of 76 lactating women receiving oxycodone immediate-release products for postpartum pain management showed that oxycodone concentrates in breastmilk with an average milk to plasma ratio of 3.2. The relative infant dose was low, approximately 1.3% of a weight-adjusted maternal dose (see Data).

In the same study, among the 70 infants exposed to oxycodone in breastmilk, no adverse events were attributed to oxycodone. However, based on known adverse effects in adults, infants should be monitored for signs of excess sedation and respiratory depression (see Clinical Considerations). There are no data on the effects of the oxycodone on milk production.

Salicylic acid has been detected in breast milk. Adverse effects on platelet function in the nursing infant exposed to aspiring in breast milk may be a potential risk. Furthermore, the risk of Reye Syndrome cause by salicylate in breast milk is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for oxycodone and aspirin tablets and any potential adverse effects on the breastfed child from oxycodone and aspirin tablets or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to oxycodone and aspirin tablets through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped or when breastfeeding is stopped.

Data

Oxycodone concentration data from 76 lactating women receiving immediate-release oxycodone products for postpartum pain management, and 28 infants exposed to oxycodone in breastmilk showed that following a median (range) dose of oxycodone in

mothers of 9.2 (5-10) mg/dose or 33.0 (5.4-59.3) mg/day, oxycodone concentrated in breastmilk with a median (range) milk to plasma ratio of 3.2 (1.2-5.3). However, when using maternal breastmilk data to estimate the daily and relative infant dose, the infant dose was 0.006 mg/kg/day, which is 1.3% of a weight-adjusted maternal dose of 10 mg every 6 hours. These estimates based on maternal breastmilk concentrations were corroborated by the observed infant concentrations, of which over 75% (19/25) were below the limit of quantification. Among the 6 infants with quantifiable concentration, the median (range) concentration was 0.2 ng/mL (0.1-0.7). These concentrations are 100 to 1000 times lower than concentrations observed in other studies after infants received oxycodone at 0.1 mg/kg/dose (~20- 200 ng/mL).

Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Pediatric Use

Oxycodone and aspirin tablets should not be administered to pediatric patients. Reye Syndrome is a rare but serious disease which can follow flu or chicken pox in children and teenagers. While the cause of Reye Syndrome is unknown, some reports claim aspirin (or salicylates) may increase the risk of developing this disease.

Geriatric Use

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 and aspirin tablets slowly in geriatric patients and frequently reevaluate the patients for signs of central nervous system and respiratory depression.

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. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to regularly evaluate renal function.

Hepatic Impairment

In a pharmacokinetic study of oxycodone in patients with end-stage liver disease, oxycodone plasma clearance decreased and the elimination half-life increased. Care should be exercised when oxycodone is used in patients with hepatic impairment.

Avoid aspirin in patients with severe hepatic impairment.

Renal Impairment

In a study of patients with end stage renal impairment, mean elimination half-life of oxycodone was prolonged in uremic patients due to increased volume of distribution and reduced clearance. Oxycodone should be used with caution in patients with renal impairment.

Avoid aspirin in patients with severe renal impairment (glomerular filtration rate less than 10 mL/minute).

ADVERSE REACTIONS

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

- Addiction, Abuse, and Misuse (see WARNINGS)
- Life-Threatening Respiratory Depression (see WARNINGS)
- Neonatal Opioid Withdrawal Syndrome (see WARNINGS)
- Opioid-Induced Hyperalgesia and Allodynia [see WARNINGS]
- Interactions with Benzodiazepines and Other CNS Depressants (see WARNINGS)
- Adrenal Insufficiency (see WARNINGS)
- Severe Hypotension (see WARNINGS)
- Gastrointestinal Adverse Reactions (see WARNINGS)
- Seizures (see WARNINGS)
- Withdrawal (see WARNINGS)

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.

Serious adverse reactions that may be associated with oxycodone and aspirin tablet use include, apnea, circulatory depression, hypotension, respiratory arrest, respiratory depression, and shock (see OVERDOSAGE).

The most frequently observed non-serious adverse reactions include lightheadedness, dizziness, drowsiness or sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

Aspirin may increase the likelihood of hemorrhage due to its effect on the gastric mucosa and platelet function. Furthermore, aspirin has the potential to cause anaphylaxis in hypersensitive patients as well as angioedema especially in patients with chronic urticaria. Other adverse reactions due to aspirin use include anorexia, reversible hepatotoxicity, leukopenia, thrombocytopenia, purpura, decreased plasma iron concentration, and shortened erythrocyte survival time.

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.

The adverse reactions obtained from postmarketing experiences with oxycodone and aspirin tablets are listed by organ system and in decreasing order of severity and/or frequency as follows:

Body as a Whole

allergic reaction, malaise, asthenia, headache, anaphylaxis, fever, hypothermia, thirst, increased sweating, accident, accidental overdose, non-accidental overdose.

Cardiovascular

tachycardia, dysrhythmias, hypotension, orthostatic hypotension, bradycardia, palpitations

Central and Peripheral Nervous System

stupor, paresthesia, agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures, anxiety, mental impairment

Fluid and Electrolyte

dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis

Gastrointestinal

hemorrhagic gastric/duodenal ulcer, gastric/peptic ulcer, dyspepsia, abdominal pain, diarrhea, eructation, dry mouth, gastrointestinal bleeding, intestinal perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye syndrome, pancreatitis, intestinal obstruction, ileus

Hearing and Vestibular

hearing loss, tinnitus. Patients with high frequency loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Hematologic

unspecified hemorrhage, purpura, reticulocytosis, prolongation of prothrombin time, disseminated intravascular coagulation, ecchymosis, thrombocytopenia

Hypersensitivity

acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria, anaphylactoid reaction

Metabolic and Nutritional

hypoglycemia, hyperglycemia, acidosis, alkalosis

Musculoskeletal rhabdomyolysis

Ocular

miosis, visual disturbances, red eye

Psychiatric

drug dependence, drug abuse, somnolence, depression, nervousness, hallucination

Reproductive

prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding, closure of patent ductus arteriosis

Respiratory System

bronchospasm, dyspnea, hyperpnea, pulmonary edema, tachypnea, aspiration, hypoventilation, laryngeal edema

Skin and Appendages

urticaria, rash, flushing, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE).

Urogenital

interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure, urinary retention

Serotonin syndrome

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis

Anaphylaxis has been reported with ingredients contained in oxycodone and aspirin tablets.

Androgen deficiency

Cases of androgen deficiency have occurred with the use of opioids for an extended period of time (see CLINICAL PHARMACOLOGY).

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see* WARNINGS*]*

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

OVERDOSAGE

Clinical Presentation

Acute overdose with oxycodone 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, hypoglycemia, 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].

Early signs of acute aspirin (salicylate) overdose including tinnitus occur at plasma concentrations approaching 200 mcg/mL. Plasma concentrations of aspirin above 300 mcg/mL are toxic. Severe toxic effects are associated with levels above 400 mcg/mL. A

single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately.

In acute salicylate overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration, and coma. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis. Serious symptoms such as depression, coma, and respiratory failure progress rapidly.

Salicylism (chronic salicylate toxicity) may be noted by symptoms such as dizziness, tinnitus, difficulty hearing, nausea, vomiting, diarrhea, and mental confusion. More severe salicylism may result in respiratory alkalosis.

Treatment of Overdose

In case of overdose, priorities are the reestablishment 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 measures.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist.

Because the duration of opioid reversal is expected to be less than the duration of action of oxycodone in oxycodone and aspirin tablets, carefully monitor the patient until spontaneous respiration is reliably re-established. 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 begun with care and by titration with smaller than usual doses of the antagonist.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions

Oxycodone and aspirin tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.

Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see* WARNINGS*].* Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of oxycodone and aspirin tablets for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial

risks.

Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.

There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see* WARNINGS*].*

Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with oxycodone and aspirin tablets. Consider this risk when selecting an initial dose and when making dose adjustments *[see* WARNINGS*].*

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with oxycodone and aspirin tablets *[see* WARNINGS, PRECAUTIONS; Information for Patients/Caregivers*]*.

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing regulations (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see* WARNINGS; Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants*]*.

Consider prescribing naloxone when the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

Initial Dosage

Initiating Treatment with Oxycodone and Aspirin Tablets

Initiate treatment with one tablet every 6 hours as needed for pain, and at lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of oxycodone and aspirin tablets. The maximum daily dose of aspirin should not exceed 4 grams or 12 tablets.

Titration and Maintenance of Therapy

Individually titrate oxycodone and aspirin tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving oxycodone and aspirin tablets to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well to reassess for the

development of addiction, abuse, or misuse (see WARNINGS). 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 and aspirin tablets dosage. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after a dosage increase), consider reducing the dosage [see WARNINGS]. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Safe Reduction or Discontinuation of Oxycodone and Aspirin Tablets

Do not abruptly discontinue oxycodone and aspirin tablets in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking oxycodone and aspirin tablets, there are a variety of factors that should be considered, including the total daily dose of opioid (including oxycodone and aspirin tablets) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with comorbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on oxycodone and aspirin tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the

opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic (see WARNINGS; Withdrawal, DRUG ABUSE AND DEPENDENCE).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Oxycodone and aspirin tablets contain oxycodone, a Schedule II controlled substance.

Abuse

Oxycodone and aspirin tablets contains oxycodone, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see WARNINGS]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of oxycodone and aspirin tablets increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of oxycodone and aspirin tablets with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of oxycodone and aspirin tablets abuse include those with a history of prolonged use of any opioid, including products containing oxycodone, those with a history of drug or alcohol abuse, or those who use oxycodone and aspirin tablets in combination with other abused drugs.

“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 people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Oxycodone and aspirin tablets, like other opioids, can be diverted for nonmedical 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 reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of Oxycodone and Aspirin Tablets

Oxycodone and aspirin tablets are for oral use only. Abuse of oxycodone and aspirin tablets poses a risk of overdose and death. The risk is increased with concurrent use oxycodone and aspirin tablets with alcohol and/or other CNS depressants.

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

Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), 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 use.

Do not abruptly discontinue oxycodone and aspirin tablets in a patient physically dependent on opioids. Rapid tapering of oxycodone and aspirin tablets in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing oxycodone and aspirin tablets, gradually taper the dosage using a patient specific plan that considers the following: the dose of oxycodone and aspirin tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at

high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper (see DOSAGE AND ADMINISTRATION, WARNINGS).

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

HOW SUPPLIED

Oxycodone and Aspirin Tablets, USP are supplied as white to off-white round biconvex tablets debossed "**€**" above bisect and "61" below bisect on one side, plain on the other side. They are available as follows:

NDC 42806-061-01 Bottles of 100

Store at 20°- 25°C (68° - 77°F); Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

DEA Order Form Required.

Store Oxycodone and Aspirin Tablets, USP securely and dispose of properly (see PRECAUTIONS; Information for Patients).

Distributed by:

Epic Pharma, LLC

Laurelton, NY 11413

Rev. 05-2025-00

MF061REV05/25

OE1245

Medication Guide

Oxycodone and Aspirin Tablets, USP
(ox-ee-CO-dohn and As-pir-in) **for oral use, CII**
Rx Only

Oxycodone and Aspirin Tablets is:

- 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 and Aspirin Tablets :

- **Get emergency help or call 911 right away if you take too much oxycodone and aspirin tablets (overdose)**. When you first start taking

oxycodone and aspirin 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. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking oxycodone and aspirin 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 and aspirin tablets. They could die from taking it. Selling or giving away oxycodone and aspirin tablets is against the law.
- Store oxycodone and aspirin tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take Oxycodone and Aspirin Tablets if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking oxycodone and aspirin tablets, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol opioid overdose, or mental health problems.

Tell your healthcare provider if you are:

- notice your pain getting worse. If your pain gets worse after you take oxycodone and aspirin tablets, do not take more of oxycodone and aspirin tablets without first talking to your healthcare provider. Talk to your healthcare provider if the pain you have increases, if you feel more sensitive to pain, or if you have new pain after taking oxycodone and aspirin tablets.
- **Are pregnant or planning to become pregnant.** Use of oxycodone and aspirin tablets for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Taking NSAID-containing products like oxycodone and aspirin tablets at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- **are breastfeeding.** oxycodone and aspirin tablets passes into breast milk and may harm your baby. Carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Seek immediate medical care if you notice these signs.
- **develop any type of rash or fever.** Contact your healthcare provider as soon

as possible and stop taking oxycodone and aspirin tablets.
- are living in a household where there are small children or someone who has abused street or prescription drugs.
- are taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking oxycodone and aspirin tablets with certain other medicines can cause serious side effects that could lead to death.

When taking Oxycodone and Aspirin Tablets:

- Do not change your dose. Take oxycodone and aspirin tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed. Take your prescribed dose at the same time every day. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- For acute (short-term) pain, you may only need to take oxycodone and aspirin tablets for a few days. You may have some oxycodone and aspirin tablets left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused oxycodone and aspirin tablets.
- Take your prescribed dose [one tablet every six hours] as needed for pain. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking oxycodone and aspirin tablets regularly, do not stop taking oxycodone and aspirin tablets without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused oxycodone and aspirin tablets by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking Oxycodone and Aspirin Tablets DO NOT:

- Drive or operate heavy machinery, until you know how oxycodone and aspirin tablets affects you. Oxycodone and aspirin tablets can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with oxycodone and aspirin tablets may cause you to overdose and die.

The possible side effects of Oxycodone and Aspirin Tablets:

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

Get emergency medical help or call 911 right away 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 and aspirin tablets. Call your healthcare provider 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**
This Medication Guide has been approved by the U.S. Food and Drug Administration.
For additional copies of the printed patient information/ medication guide, please visit www.epic-pharma.com or call 1-888-374-2791.

Distributed by:

Epic Pharma, LLC

Laurelton, NY 11413

Rev. 05-2025-00

OE2935

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Oxycodone Hydrochloride, USP CII

4.8355 mg*/325 mg

Rx Only

100 Tablets

OXYCODONE AND ASPIRIN

oxycodone and aspirin tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42806-061
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OXYCODONE HYDROCHLORIDE (UNII: C1ENJ2TE6C) (OXYCODONE - UNII:CD35PMG570)	OXYCODONE HYDROCHLORIDE	4.8355 mg
ASPIRIN (UNII: R16CO5Y76E) (ASPIRIN - UNII:R16CO5Y76E)	ASPIRIN	325 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
ZINC STEARATE (UNII: H92E6QA4FV)	

Product Characteristics

Color	WHITE (off-white)	**Score**	2 pieces
Shape	ROUND (biconvex)	**Size**	12mm
Flavor		**Imprint Code**	E61
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42806-061-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/30/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040910	06/30/2020	

Labeler - Epic Pharma, LLC (827915443)

Registrant - Epic Pharma, LLC (827915443)

Establishment

Name	Address	ID/FEI	Business Operations
Epic Pharma, LLC		827915443	MANUFACTURE(42806-061)

Revised: 12/2025 Epic Pharma, LLC