Oxycodone and Acetaminophen Tablets, USP Rx only

8182824 R8

OXYCODONE AND ACETAMINOPHEN TABLETS, USP
7.5 mg/325 mg and 10 mg/325 mg CII
Rx only

BOXED WARNING

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

Oxycodone and acetaminophen tablets expose 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 oxycodone and acetaminophen tablets, and monitor all patients regularly for the development of these behaviors or conditions (see WARNINGS).

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of oxycodone and acetaminophen tablets. Monitor for respiratory depression, especially during initiation of oxycodone and acetaminophen tablets or following a dose increase (see WARNINGS).

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of oxycodone and acetaminophen tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see WARNINGS).

Cytochrome P450 3A4 Interaction

The concomitant use of oxycodone and acetaminophen tablets with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone and acetaminophen tablets 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 and acetaminophen tablets plasma concentration. Monitor patients receiving oxycodone and acetaminophen tablets and any CYP3A4 inhibitor or inducer (see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions).

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product (see WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE).

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS, PRECAUTIONS; Drug Interactions).

- **Reserve concomitant prescribing of oxycodone and acetaminophen tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

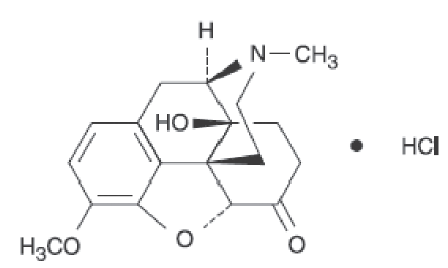
DESCRIPTION

Each tablet, for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:

Oxycodone hydrochloride, USP.. 7.5 mg
(equivalent to 6.7228 mg of Oxycodone)
Acetaminophen, USP .... 325 mg
Oxycodone hydrochloride, USP .... 10 mg
(equivalent to 8.9637 mg of Oxycodone)
Acetaminophen, USP .... 325 mg

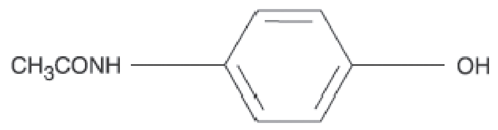
In addition each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, FD&C Yellow #5 Aluminum Lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized corn starch and stearic acid. May also contain corn starch and / or crospovidone.

Oxycodone, 14-hydroxydihydrocodeinone, is a semisynthetic opioid analgesic which occurs as a white, odorless, crystalline powder having a saline, bitter taste. The molecular formula for oxycodone hydrochloride is $C_{18}H_{21}NO_4$•HCl and the molecular weight 351.82. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



$C_{18}H_{21}NO_4$•HCl MW 351.82

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. The molecular formula for acetaminophen is $C_8H_9NO_2$ and the molecular weight is 151.16. It may be represented by the following structural formula:



$C_8H_9NO_2$ MW 151.16

CLINICAL PHARMACOLOGY

Central Nervous System

Oxycodone is a semisynthetic pure opioid agonist whose principal therapeutic action is analgesia. Other pharmacological effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. These effects are mediated by receptors (notably μ and κ) in the central nervous system for endogenous opioid-like compounds such as endorphins and enkephalins. Oxycodone produces respiratory depression through direct activity at respiratory centers in the brain stem and depresses the cough reflex by direct effect on the center of the medulla.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic. The site and mechanism for the analgesic effect of acetaminophen has not been determined. The antipyretic effect of acetaminophen is accomplished through the inhibition of endogenous pyrogen action on the hypothalamic heat-regulating centers.

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone reduces motility by increasing smooth muscle tone in the stomach and duodenum. In the small intestine, digestion of food is delayed by decreases in propulsive contractions. Other opioid effects include contraction of biliary tract smooth muscle, spasm of the Sphincter of Oddi, increased ureteral and bladder sphincter tone, and a reduction in uterine tone.

Cardiovascular System

Oxycodone may produce a release of histamine and may be associated with orthostatic hypotension, and other symptoms, such as pruritus, flushing, red eyes, and sweating.

Pharmacokinetics

Absorption and Distribution

The mean absolute oral bioavailability of oxycodone in cancer patients was reported to be about 87%. Oxycodone has been shown to be 45% bound to human plasma proteins *in vitro*. The volume of distribution after intravenous administration is 211.9 ± 186.6 L.

Absorption of acetaminophen is rapid and almost complete from the GI tract after oral administration. With overdosage, absorption is complete in 4 hours. Acetaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; only 20% to 50% may be bound at the concentrations encountered during acute intoxication.

Metabolism and Elimination

A high portion of oxycodone is N-dealkylated to noroxycodone during first-pass metabolism.

Oxymorphone, is formed by the O-demethylation of oxycodone. The metabolism of oxycodone to oxymorphone is catalyzed by CYP2D6. 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. Following a single, oral dose of oxycodone, the mean ± SD elimination half-life is 3.51 ± 1.43 hours.

Acetaminophen is metabolized in the liver via cytochrome P450 microsomal enzyme. About 80 to 85% of the acetaminophen in the body is conjugated principally with glucuronic acid and to a lesser extent with sulfuric acid and cysteine. After hepatic conjugation, 90 to 100% of the drug is recovered in the urine within the first day.

About 4% of acetaminophen is metabolized via cytochrome P450 oxidase to a toxic metabolite which is further detoxified by conjugation with glutathione, present in a fixed amount. It is believed that the toxic metabolite NAPQI (N acetyl-p-benzoquinoneimine, N-acetylimidoquinone) is responsible for liver necrosis. High doses of acetaminophen may deplete the glutathione stores so that inactivation of the toxic metabolite is decreased. At high doses, the capacity of metabolic pathways for conjugation with glucuronic acid and sulfuric acid may be exceeded, resulting in increased metabolism of acetaminophen by alternate pathways.

INDICATIONS AND USAGE

Oxycodone and acetaminophen tablets, USP are indicated for the management of moderate to moderately severe 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, even at recommended doses (see **WARNINGS**), reserve oxycodone and acetaminophen 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

CONTRAINDICATIONS

Oxycodone and acetaminophen 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 hypersensitivity to oxycodone, acetaminophen, or any other component of this product
- Hypercarbia
- Known or suspected paralytic ileus

WARNINGS

Addiction, Abuse, and Misuse

Oxycodone and acetaminophen tablets contain oxycodone, a Schedule II controlled substance. As an opioid, oxycodone and acetaminophen tablets expose 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 acetaminophen 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 acetaminophen tablets, and monitor all patients receiving oxycodone and acetaminophen tablets for the development of these behaviors or 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 acetaminophen tablets, but use in such patients necessitates intensive counseling about the risks and proper use of oxycodone and acetaminophen tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing oxycodone and acetaminophen tablets.

Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug (see **PRECAUTIONS; Information for Patients**). 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 acetaminophen tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of oxycodone and acetaminophen tablets.

To reduce the risk of respiratory depression, proper dosing and titration of oxycodone and acetaminophen tablets are essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the oxycodone and acetaminophen tablets dosage 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 acetaminophen tablets, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of oxycodone and acetaminophen tablets 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. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see **PRECAUTIONS; Information for Patients, Pregnancy**).

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

Concomitant use of oxycodone and acetaminophen 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 acetaminophen tablets 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 acetaminophen tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in oxycodone and acetaminophen tablets-treated patients may increase oxycodone and acetaminophen tablets plasma concentrations and prolong opioid adverse reactions. When using oxycodone and acetaminophen tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in oxycodone and acetaminophen tablets-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of oxycodone and acetaminophen tablets until stable drug effects are achieved (see **PRECAUTIONS; Drug Interactions**).

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

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 acetaminophen tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar 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. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when oxycodone and acetaminophen tablets are 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** and **PRECAUTIONS; Information for Patients**).

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

The use of oxycodone and acetaminophen 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 acetaminophen 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 acetaminophen tablets (see **WARNINGS**).

Elderly, Cachetic, 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**).

Monitor such patients closely, particularly when initiating and titrating oxycodone and acetaminophen tablets and when oxycodone and acetaminophen tablets are 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.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of worsening in patients with head injuries.

Hypotensive Effect

Oxycodone may cause severe hypotension particularly in individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs which compromise vasomotor tone such as phenothiazines. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure. Oxycodone may produce orthostatic hypotension in ambulatory patients.

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen per day, even if they feel well.

Serious skin reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hypersensitivity/anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs including swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue Oxycodone and Acetaminophen Tablets, USP immediately and seek medical care if they experience these symptoms. Do not prescribe Oxycodone and Acetaminophen Tablets, USP for patients with acetaminophen allergy.

PRECAUTIONS

General

Oxycodone and Acetaminophen Tablets 7.5 mg/325 mg and 10 mg/325 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Opioid analgesics should be used with caution when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Acute Abdominal Conditions: The administration of oxycodone and acetaminophen tablets or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Oxycodone and acetaminophen tablets should be given with caution to patients with CNS depression, elderly or debilitated patients, patients with severe impairment of hepatic, pulmonary, or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, urethral stricture, acute alcoholism, delirium tremens, kyphoscoliosis with respiratory depression, myxedema, and toxic psychosis.

Oxycodone and acetaminophen tablets may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Following administration of oxycodone and acetaminophen tablets, anaphylactic reactions have been reported in patients with a known hypersensitivity to codeine, a compound with a structure similar to morphine and oxycodone. The frequency of this possible cross-sensitivity is unknown.

Interactions with Other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, centrally-acting anti-emetics, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone and acetaminophen tablets may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

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.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the Sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

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

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Discontinuation of Oxycodone and Acetaminophen Tablets**).

Information for Patients

The following information should be provided to patients receiving oxycodone and acetaminophen tablets by their physician, nurse, pharmacist, or caregiver:

1. Do not take oxycodone and acetaminophen tablets if you are allergic to any of its ingredients.
2. If you develop signs of allergy such as a rash or difficulty breathing stop taking oxycodone and acetaminophen tablets and contact your healthcare provider immediately.
3. Do not take more than 4000 milligrams of acetaminophen per day. Call your doctor if you took more than the recommended dose.
4. Patients should be aware that oxycodone and acetaminophen tablets contain oxycodone, which is a morphine-like substance.
5. Patients should be instructed to keep oxycodone and acetaminophen tablets in a secure place out of the reach of children. In the case of accidental ingestions, emergency medical care should be sought immediately.
6. When oxycodone and acetaminophen tablets are no longer needed, the unused tablets should be destroyed by flushing down the toilet.
7. Patients should be advised not to adjust the medication dose themselves. Instead, they must consult with their prescribing physician.
8. Patients should be advised that oxycodone and acetaminophen tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
9. Patients should not combine oxycodone and acetaminophen tablets with alcohol, opioid analgesics, tranquilizers, sedatives, or other CNS depressants unless under the recommendation and guidance of a physician. When co-administered with another CNS depressant, oxycodone and acetaminophen tablets can cause dangerous additive central nervous system or respiratory depression, which can result in serious injury or death.
10. The safe use of oxycodone and acetaminophen tablets during pregnancy has not been established; thus, women who are planning to become pregnant or are pregnant should consult with their physician before taking oxycodone and acetaminophen tablets.
11. Nursing mothers should consult with their physicians about whether to discontinue nursing or discontinue oxycodone and acetaminophen tablets because of the potential for serious adverse reactions to nursing infants.
12. Patients who are treated with oxycodone and acetaminophen tablets for more than a few weeks should be advised not to abruptly discontinue the medication. Patients should consult with their physician for a gradual discontinuation dose schedule to taper off the medication.
13. Patients should be advised that oxycodone and acetaminophen tablets are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

Addiction, Abuse, and Misuse

Inform patients that the use of oxycodone and acetaminophen 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 acetaminophen tablets with others and to take steps to protect oxycodone and acetaminophen 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 acetaminophen tablets or when the dosage is increased, and that it can occur even at recommended dosages (see **WARNINGS**). Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death (see **WARNINGS**). Instruct patients to take steps to store oxycodone and acetaminophen tablets securely and to dispose of unused oxycodone and acetaminophen tablets by flushing down the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if oxycodone and acetaminophen tablets are used with benzodiazepines or other CNS depressants, including

Medication Guide
OXYCODONE (ox'' i koe' done) AND ACETAMINOPHEN (a seet'' a min' oh fen) TABLETS CII

Oxycodone and acetaminophen tablets are:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage moderate to moderately severe pain, severe enough to require an opioid analgesic, 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 acetaminophen tablets:
- **Get emergency help right away if you take too many oxycodone and acetaminophen tablets (overdose)**. When you first start taking oxycodone and acetaminophen tablets, when your dose is changed, or if you take too many (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking oxycodone and acetaminophen 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 acetaminophen tablets. They could die from taking it. Store oxycodone and acetaminophen tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away oxycodone and acetaminophen tablets is against the law.

Do not take oxycodone and acetaminophen tablets if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- known hypersensitivity to oxycodone, acetaminophen, or any other component of this product.
- hypercarbia.

Before taking oxycodone and acetaminophen 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 addiction, or mental health problems.

Tell your healthcare provider if you are:
- **pregnant or planning to become pregnant.** Prolonged use of oxycodone and acetaminophen tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Oxycodone and acetaminophen tablets pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking oxycodone and acetaminophen tablets with certain other medicines can cause serious side effects that could lead to death.

When taking oxycodone and acetaminophen tablets:
- Do not change your dose. Take oxycodone and acetaminophen tablets exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 6 hours 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.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking oxycodone and acetaminophen tablets regularly, do not stop taking oxycodone and acetaminophen tablets without talking to your healthcare provider.
- After you stop taking oxycodone and acetaminophen tablets, dispose of unused tablets by flushing down the toilet.

While taking oxycodone and acetaminophen tablets DO NOT:
- Drive or operate heavy machinery, until you know how oxycodone and acetaminophen tablets affect you. Oxycodone and acetaminophen 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 acetaminophen tablets may cause you to overdose and die.

Medication Guide
OXYCODONE (ox'' i koe' done) AND ACETAMINOPHEN (a seet'' a min' oh fen) TABLETS CII

Oxycodone and acetaminophen tablets are:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage moderate to moderately severe pain, severe enough to require an opioid analgesic, 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 acetaminophen tablets:
- **Get emergency help right away if you take too many oxycodone and acetaminophen tablets (overdose)**. When you first start taking oxycodone and acetaminophen tablets, when your dose is changed, or if you take too many (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking oxycodone and acetaminophen 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 acetaminophen tablets. They could die from taking it. Store oxycodone and acetaminophen tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away oxycodone and acetaminophen tablets is against the law.

Do not take oxycodone and acetaminophen tablets if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- known hypersensitivity to oxycodone, acetaminophen, or any other component of this product.
- hypercarbia.

Before taking oxycodone and acetaminophen 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 addiction, or mental health problems.

Tell your healthcare provider if you are:
- **pregnant or planning to become pregnant.** Prolonged use of oxycodone and acetaminophen tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Oxycodone and acetaminophen tablets pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking oxycodone and acetaminophen tablets with certain other medicines can cause serious side effects that could lead to death.

When taking oxycodone and acetaminophen tablets:
- Do not change your dose. Take oxycodone and acetaminophen tablets exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 6 hours 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.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking oxycodone and acetaminophen tablets regularly, do not stop taking oxycodone and acetaminophen tablets without talking to your healthcare provider.
- After you stop taking oxycodone and acetaminophen tablets, dispose of unused tablets by flushing down the toilet.

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- problems urinating • pancreas or gallbladder problems
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The possible side effects of oxycodone and acetaminophen tablets:

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

Get emergency medical help if you have:

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

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

Manufactured for: **Qualitest Pharmaceuticals Huntsville, AL, 35811** call 1-800-444-4011

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

Issued: 8/2016
R1 8183822

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alcohol, and not to use these concomitantly unless supervised by a health care provider (see **WARNINGS** and **PRECAUTIONS; Drug Interactions**).

Serotonin Syndrome

Inform patients that oxycodone and acetaminophen tablets could cause a rare but potentially life-threatening condition 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 (see **PRECAUTIONS; Drug Interactions**).

Adrenal Insufficiency

Inform patients that oxycodone and acetaminophen 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**).

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform patients that prolonged use of oxycodone and acetaminophen tablets 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 acetaminophen tablets can cause fetal harm and to inform the prescriber of a known or suspected pregnancy (see **PRECAUTIONS; Pregnancy**).

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs (see **PRECAUTIONS; Nursing Mothers**).

Disposal of Unused Oxycodone and Acetaminophen Tablets

Advise patients to dispose of unused tablets by flushing down the toilet.

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.

Drug Interactions

CYP3A4

Inhibitor

The concomitant use of oxycodone and acetaminophen tablets and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g., ritonavir), can increase the plasma concentration of oxycodone and acetaminophen tablets, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of oxycodone and acetaminophen tablets and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of oxycodone and acetaminophen tablets is achieved (see **WARNINGS**).

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone and acetaminophen tablets 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 and acetaminophen tablets.

If concomitant use is necessary, consider dosage reduction of oxycodone and acetaminophen tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the oxycodone and acetaminophen tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

Inducer

The concomitant use of oxycodone and acetaminophen tablets and CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, can decrease the plasma concentration of oxycodone and acetaminophen tablets (see **CLINICAL PHARMACOLOGY**), resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone and acetaminophen tablets (see **WARNINGS**).

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone and acetaminophen tablets 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.

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

Benzodiazepines and other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS**).

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as 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), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome (see **PRECAUTIONS; Information for Patients**).

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue oxycodone and acetaminophen tablets if serotonin syndrome is suspected.

Drug/Drug Interactions with Oxycodone

Opioid analgesics may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increase in the degree of respiratory depression.

Patients receiving CNS depressants such as other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, centrally-acting anti-emetics, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone and acetaminophen tablets may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. The concurrent use of anticholinergics with opioids may produce paralytic ileus.

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, naltrexone, and butorphanol) should be administered with caution to a patient who has received or is receiving a pure opioid agonist such as oxycodone. These agonist/antagonist analgesics may reduce the analgesic effect of oxycodone or may precipitate withdrawal symptoms.

Drug/Drug Interactions with Acetaminophen

Alcohol, Ethyl: Hepatotoxicity has occurred in chronic alcoholics following various dose levels (moderate to excessive) of acetaminophen.

Anticholinergics: The onset of acetaminophen effect may be delayed or decreased slightly, but the ultimate pharmacological effect is not significantly affected by anticholinergics.

Oral Contraceptives: Increase in glucuronidation resulting in increased plasma clearance and a decreased half-life of acetaminophen.

Charcoal (Activated): Reduces acetaminophen absorption when administered as soon as possible after overdose.

Beta Blockers (Propanolol): Propranolol appears to inhibit the enzyme systems responsible for the glucuronidation and oxidation of acetaminophen. Therefore, the pharmacologic effects of acetaminophen may be increased.

Loop Diuretics: The effects of the loop diuretic may be decreased because acetaminophen may decrease renal prostaglandin excretion and decrease plasma renin activity.

Lamotrigine: Serum lamotrigine concentrations may be reduced, producing a decrease in therapeutic effects.

Probenecid: Probenecid may increase the therapeutic effectiveness of acetaminophen slightly.

Zidovudine: The pharmacologic effects of zidovudine may be decreased because of enhanced non-hepatic or renal clearance of zidovudine.

Drug/Laboratory Test Interactions

Depending on the sensitivity/specificity and the test methodology, the individual components of oxycodone and acetaminophen 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. Acetaminophen may interfere with home blood glucose measurement systems; decreases of > 20% in mean glucose values may be noted. This effect appears to be drug, concentration and system dependent.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Animal studies to evaluate the carcinogenic potential of oxycodone and acetaminophen have not been performed.

Mutagenesis: The combination of oxycodone and acetaminophen 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.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (see **ADVERSE REACTIONS**).

Pregnancy

Teratogenic Effects: Pregnancy Category C: Animal reproductive studies have not been conducted with oxycodone and acetaminophen tablets. It is also not known whether oxycodone and acetaminophen tablets can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Oxycodone and acetaminophen tablets should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Fetal/Neonatal Adverse Reactions: Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents 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**).

Labor and Delivery

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to oxycodone and acetaminophen tablets. 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 acetaminophen tablets slowly in geriatric patients (see **WARNINGS**).

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.

Renal Impairment

In a study of patients with end-stage renal impairment, mean elimination half-life 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.

ADVERSE REACTIONS

Postmarketing Experience

Serious adverse reactions that may be associated with oxycodone and acetaminophen tablet use include adrenal insufficiency, respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, serotonin syndrome, and shock (see **OVERDOSAGE**).

Androgen deficiency

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms of hypogonadism, such as impotence, erectile dysfunction, or amenorrhea. The causal role of opioids in the 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. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

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.

Hypersensitivity reactions may include: Skin eruptions, urticarial, erythematous skin reactions.

Hematologic reactions may include: Thrombocytopenia, neutropenia, pancytopenia, hemolytic anemia. Rare cases of agranulocytosis has likewise been associated with acetaminophen use. In high doses, the most serious adverse effect is a dose-dependent, potentially fatal hepatic necrosis. Renal tubular necrosis and hypoglycemic coma also may occur.

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

Body as a Whole

Anaphylactoid reaction, allergic reaction, malaise, asthenia, fatigue, chest pain, fever, hypothermia, thirst, headache, increased sweating, accidental overdose, non-accidental overdose

Cardiovascular

Hypotension, hypertension, tachycardia, orthostatic hypotension, bradycardia, palpitations, dysrhythmias

Central and Peripheral Nervous System

Stupor, tremor, paraesthesia, hypoaesthesia, lethargy, seizures, anxiety, mental impairment, agitation, cerebral edema, confusion, dizziness

Fluid and Electrolyte

Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis

Gastrointestinal

Dyspepsia, taste disturbances, abdominal pain, abdominal distention, sweating increased, diarrhea, dry mouth, flatulence, gastrointestinal disorder, nausea, vomiting, pancreatitis, intestinal obstruction, ileus

Hepatic

Transient elevations of hepatic enzymes, increase in bilirubin, hepatitis, hepatic failure, jaundice, hepatotoxicity, hepatic disorder

Hearing and Vestibular

Hearing loss, tinnitus

Hematologic

Thrombocytopenia

Hypersensitivity

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

Metabolic and Nutritional

Hypoglycemia, hyperglycemia, acidosis, alkalosis

Musculoskeletal

Myalgia, rhabdomyolysis

Ocular

Miosis, visual disturbances, red eye

Psychiatric

Drug dependence, drug abuse, insomnia, confusion, anxiety, agitation, depressed level of consciousness, nervousness, hallucination, somnolence, depression, suicide

Respiratory System

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

Skin and Appendages

Erythema, urticaria, rash, flushing

Urogenital

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

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

Abuse

Oxycodone and acetaminophen tablets contain oxycodone, a substance with a high potential for abuse similar to other opioids including morphine and other opioids used in analgesia. Oxycodone and acetaminophen tablets can be abused and are subject to misuse, addiction, and criminal diversion (see **WARNINGS**).

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

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

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

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

Oxycodone and acetaminophen tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of Oxycodone and Acetaminophen Tablets

Oxycodone and acetaminophen tablets are for oral use only. Abuse of oxycodone and acetaminophen tablets poses a risk of overdose and death.

Dependence

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

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

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

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs (see **PRECAUTIONS; Pregnancy**).

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

OVERDOSAGE

Following an acute overdosage, toxicity may result from the oxycodone or the acetaminophen.

Clinical Presentation

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

In *acetaminophen* overdosage: dose-dependent potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and coagulation defects may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment of Overdose

Oxycodone

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 techniques.

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

Because the duration of opioid reversal is expected to be less than the duration of action of oxycodone in oxycodone and acetaminophen 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.

Acetaminophen

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading.

To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse (see **WARNINGS**).

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with oxycodone and acetaminophen tablets and adjust the dosage accordingly (see **WARNINGS**).

Initial Dosage

Initiating Treatment with Oxycodone and Acetaminophen Tablets

Initiate treatment with oxycodone and acetaminophen tablets 7.5 mg/ 325 mg, adult dosage, with one tablet every 6 hours as needed for pain. Initiate treatment with oxycodone and acetaminophen tablets 10 mg/ 325 mg, adult dosage, with one tablet every 6 hours as needed for pain.

The total daily dose of acetaminophen should not exceed 4 grams.

Strength	Maximal Daily Dose
Oxycodone and acetaminophen 7.5 mg/325 mg	8 Tablets
Oxycodone and acetaminophen 10 mg/325 mg	6 Tablets

Titration and Maintenance of Therapy

Individually titrate oxycodone and acetaminophen tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving oxycodone and acetaminophen tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse (see **WARNINGS**). 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 acetaminophen tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Discontinuation of Oxycodone and Acetaminophen Tablets

When a patient who has been taking oxycodone and acetaminophen tablets regularly and may be physically dependent no longer requires therapy with oxycodone and acetaminophen tablets, use a gradual downward titration of the dosage to prevent signs and symptoms of withdrawal. Do not stop oxycodone and acetaminophen tablets abruptly (see **WARNINGS, DRUG ABUSE AND DEPENDENCE**).

HOW SUPPLIED

Oxycodone and Acetaminophen Tablets, USP, 7.5 mg/325 mg, supplied as a yellow, oblong, flat faced beveled edge tablet, debossed "4827" on one side and debossed "V" on the reverse side, are available as follows:

- Bottles of 100: NDC 0603-4979-21
- Bottles of 500: NDC 0603-4979-28

Oxycodone and Acetaminophen Tablets, USP, 10 mg/325 mg, supplied as a yellow, oblong, flat faced beveled edge tablet, debossed "4829" on one side and debossed "V" on the reverse side, are available as follows:

- Bottles of 100: NDC 0603-4982-21
- Bottles of 500: NDC 0603-4982-28

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

DISPENSE in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

DEA Order Form Required.

Manufactured for:
QUALITEST PHARMACEUTICALS
Huntsville, AL 35811

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