

**WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATO TOXICITY; 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 and conditions [see WARNINGS].

#### Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see WARNINGS]. 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

- complete a REMS-compliant education program.
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products.
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

#### 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 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 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. Monitor patients receiving oxycodone and acetaminophen tablets and any CYP3A4 inhibitor or inducer [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

#### Hepatology

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 mg per day, and often involve more than one acetaminophen-containing product.

#### 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

Oxycodone hydrochloride and acetaminophen are available in tablets for oral administration.

Each Oxycodone and Acetaminophen Tablet, 2.5 mg/300 mg contains:

Oxycodone Hydrochloride USP ..... 2.5 mg\*  
(\* 2.5 mg Oxycodone Hydrochloride is equivalent to 2.2409 mg Oxycodone)  
Acetaminophen USP ..... 300 mg

Each Oxycodone and Acetaminophen Tablet, 5 mg/300 mg contains:

Oxycodone Hydrochloride USP ..... 5 mg\*  
(\* 5 mg Oxycodone Hydrochloride is equivalent to 4.4815 mg Oxycodone)  
Acetaminophen USP ..... 300 mg

Each Oxycodone and Acetaminophen Tablet, 7.5 mg/300 mg contains:

Oxycodone Hydrochloride USP ..... 7.5 mg\*  
(\* 7.5 mg Oxycodone Hydrochloride is equivalent to 6.7228 mg Oxycodone)  
Acetaminophen USP ..... 300 mg

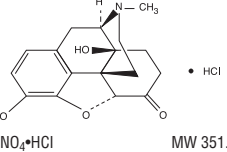
Each Oxycodone and Acetaminophen Tablet, 10 mg/300 mg contains:

Oxycodone Hydrochloride USP ..... 10 mg\*  
(\* 10 mg Oxycodone Hydrochloride is equivalent to 8.9637 mg Oxycodone)  
Acetaminophen USP ..... 300 mg

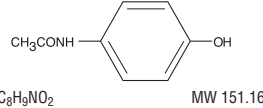
#### Inactive Ingredients

The tablets contain: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, croscollin, pregelatinized starch, and stearic acid. In addition, the 2.5 mg/300 mg strength contains FD&C Blue #1 Aluminum Lake; the 5 mg/300 mg strength contains D&C Yellow #10; the 7.5 mg/300 mg strength contains FD&C Red #40 Aluminum Lake; the 10 mg/300 mg strength contains FD&C Yellow #6 Aluminum Lake.

Oxycodone and acetaminophen tablets contain oxycodone, 14-hydroxydihydrocodeinone, a semisynthetic opioid analgesic which occurs as a white to off-white fine crystalline powder. The molecular formula for oxycodone hydrochloride is C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>•HCl and the molecular weight is 351.82. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



Oxycodone and acetaminophen tablets contain acetaminophen, 4'-hydroxyacetanilide, a non-opiate, non-salty/late analgesic and antipyretic which occurs as a white, odorless, crystalline powder. The molecular formula for acetaminophen is C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub> and the molecular weight is 151.16. It may be represented by the following structural formula:



#### CLINICAL PHARMACOLOGY

##### Mechanism of Action

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

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

The precise mechanism of the analgesic properties of acetaminophen is not established but is thought to involve central actions.

##### 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 both increases in carbon dioxide tension and electrical stimulation.

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

Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

##### 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.

##### 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, sweating, and/or orthostatic hypotension.

##### Effects on the Endocrine System

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

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. 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 [see ADVERSE REACTIONS].

##### Effects on the Immune System

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

##### Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. 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].

##### 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 overdose, 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

###### Oxycodone

In humans, oxycodone is extensively metabolized to noroxycodone by means of CYP3A-mediated N-demethylation, oxycodone by means of CYP2D6-mediated O-demethylation, and their glucuronides [see PRECAUTIONS; Drug Interactions].

###### Acetaminophen

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. A small fraction (10-25%) of acetaminophen is bound to plasma proteins. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdose. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via the cytochrome P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. See OVERDOSAGE for toxicity information.

#### INDICATIONS AND USAGE

Oxycodone and acetaminophen 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, 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 or suspected gastrointestinal obstruction, including paralytic ileus [see WARNINGS]
- Hypersensitivity to oxycodone, acetaminophen, or any other component of the product (e.g., anaphylaxis) [see WARNINGS, ADVERSE REACTIONS]

#### 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].

Because 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 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 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. Consider prescribing naloxone for the emergency treatment of opioid overdose [see WARNINGS, Life-Threatening Respiratory Depression, DOSAGE AND ADMINISTRATION; Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose].

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/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.

##### Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to 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/OpioidAnalgesicsREMSPCG](http://www.fda.gov/OpioidAnalgesicsREMSPCG).
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 800-503-0784, or log on to [www.opioidanalgesicsrems.com](http://www.opioidanalgesicsrems.com). The FDA Blueprint can be found at [www.fda.gov/OpioidAnalgesicsREMSBlueprint](http://www.fda.gov/OpioidAnalgesicsREMSBlueprint).

#### 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<sub>2</sub>) 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 to 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 oxycodone and acetaminophen tablets, especially by children, can result in respiratory depression and death due to an overdose of oxycodone and acetaminophen tablets.

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].

##### Effects on the Immune System

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].

##### 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 acetaminophen 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; Addiction, Abuse, and Misuse, Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants; PRECAUTIONS; Information for Patients/Caregivers].

##### 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see PRECAUTIONS; Information for Patients/Caregivers, 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 hydrochloride 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 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 increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see PRECAUTIONS; Drug Interactions].

Concomitant use of oxycodone and acetaminophen tablets with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone hydrochloride plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone hydrochloride. 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].

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

#### 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.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see WARNINGS, Life-Threatening Respiratory Depression, DOSAGE AND ADMINISTRATION; Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose].

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.

#### 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, Life-Threatening Respiratory Depression].

**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, Life-Threatening Respiratory Depression].

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, Life-Threatening Respiratory Depression]. 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 one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Warn 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 acetaminophen 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) [see PRECAUTIONS; Drug Interactions]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of oxycodone and acetaminophen tablets. In patients with circulatory shock oxycodone and acetaminophen tablets may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of oxycodone and acetaminophen tablets with circulatory shock.

#### Hepatotoxicity

Oxycodone 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.

Inform 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 the 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 included swelling of the face, mouth, and throat, and 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 immediately and seek medical care if they experience these symptoms. Do not prescribe oxycodone and acetaminophen tablets for patients with known allergic allergy [see PRECAUTIONS; Information for Patients/Caregivers].

**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<sub>2</sub> retention (e.g., those with evidence of increased intracranial pressure or brain tumors), oxycodone and acetaminophen tablets may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with oxycodone and acetaminophen tablets.

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

#### Risks of Use in Patients with Gastrointestinal Conditions

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

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

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

#### Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in oxycodone and acetaminophen 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. Monitor patients with a history of seizure disorders for worsened seizure control during oxycodone and acetaminophen tablets therapy.

#### Withdrawal

Do not abruptly discontinue oxycodone and acetaminophen tablets in a patient physically dependent on opioids. When discontinuing oxycodone and acetaminophen tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone and acetaminophen tablets 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].



## MEDICATION GUIDE

### Oxycodone (ox' i koe' done) and Acetaminophen (a see't 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 pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate and 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 or call 911 right away if you take too much Oxycodone and Acetaminophen Tablets (overdose).** When you first start taking Oxycodone and Acetaminophen 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 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. Selling or giving away Oxycodone and Acetaminophen Tablets is against the law.
- Store Oxycodone and Acetaminophen 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 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 ingredient in Oxycodone and Acetaminophen Tablets

#### 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, opioid overdose, 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.
- Living in a household where there are small children or someone who has abused street or prescription drugs.
- 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. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 6 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 Acetaminophen Tablets regularly, do not stop taking Oxycodone and Acetaminophen Tablets without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused Oxycodone and Acetaminophen Tablets by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal) for additional information on disposal of unused medicines.

#### 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.

#### 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 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 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](http://dailymed.nlm.nih.gov)**

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