

## MEDICATION GUIDE

### PROLATE

#### Oxycodone Hydrochloride and Acetaminophen Oral Solution, CI

#### Prolate is:

- 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 Prolate:

- Get emergency help or call 911 right away if you take too much Prolate (overdose).** When you first start taking Prolate, 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. Taking Prolate 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. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Never give anyone else your Prolate. They could die from taking it. Selling or giving away Prolate is against the law.
- Store Prolate securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

#### Do not take Prolate 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 Prolate

#### Before taking Prolate, 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 Prolate during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- Breastfeeding.** Prolate passes 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 Prolate with certain other medicines can cause serious side effects that could lead to death.

#### When taking Prolate:

- Do not change your dose. Take Prolate exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Ask your healthcare provider if you have any questions on how to correctly measure your dose. Always use a calibrated measuring device for Prolate to correctly measure your dose. A household teaspoon or tablespoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the possibility of using a tablespoon instead of a teaspoon, which could lead to overdose, it is strongly recommended that caregivers obtain and use a calibrated measuring device.
- 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 Prolate regularly, do not stop taking Prolate without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused Prolate 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 Prolate DO NOT:

- Drive or operate heavy machinery, until you know how Prolate affects you. Prolate 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 Prolate may cause you to overdose and die.

**WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); 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**

#### Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering oxycodone hydrochloride and acetaminophen oral solution. Dosing errors due to confusion between mg and mL, and other oxycodone hydrochloride and acetaminophen solutions of different concentrations can result in accidental overdose and death [see WARNINGS, DOSAGE AND ADMINISTRATION].

#### Addiction, Abuse, and Misuse

Oxycodone hydrochloride and acetaminophen oral solution exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing oxycodone hydrochloride and acetaminophen oral solution, 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 hydrochloride and acetaminophen oral solution. Monitor for respiratory depression, especially during initiation of oxycodone hydrochloride and acetaminophen oral solution or following a dose increase [see WARNINGS].

#### Accidental Ingestion

Accidental ingestion of oxycodone hydrochloride and acetaminophen oral solution, especially by children, can result in a fatal overdose of oxycodone hydrochloride and acetaminophen oral solution [see WARNINGS].

#### Neonatal Opioid Withdrawal Syndrome

Prolonged use of oxycodone hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution 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 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 hydrochloride and acetaminophen oral solution 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 liquid form for oral administration.

Each 5 mL of Prolate for oral administration contains:

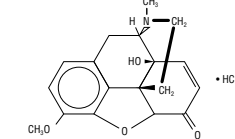
Oxycodone hydrochloride USP ..... 10 mg\*
(\*10 mg oxycodone hydrochloride is equivalent to 8.9637 mg oxycodone)

Acetaminophen USP ..... 300 mg

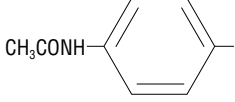
#### Inactive Ingredients

The solution contains: anhydrous citric acid, edetate disodium, fructose, glycerin, polyethylene glycol, potassium sorbate, propylene glycol, purified water, saccharin sodium with FD&C Red #40 as coloring and tropical fruit punch flavoring.

Oxycodone hydrochloride and acetaminophen oral solution contains 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>25</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 hydrochloride and acetaminophen oral solution contains acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate 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 151.17. 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 miosis 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, oxymorphone 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 glucuronic acid 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 hydrochloride and acetaminophen oral solution is 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 hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution is 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

#### Risk of Accidental Overdose and Death due to Medication Errors

Drugging errors can result in accidental overdose and death. Avoid dosing errors that may result from confusion between mg and mL and confusion with oxycodone hydrochloride and acetaminophen oral solutions of different concentrations, when prescribing, dispensing, and administering oxycodone hydrochloride and acetaminophen oral solution. Ensure that the dose is communicated clearly and dispensed accurately. Always use a calibrated measuring device when administering oxycodone hydrochloride and acetaminophen oral solution to ensure the dose is measured and administered accurately.

#### Addition, Abuse, and Misuse

Oxycodone hydrochloride and acetaminophen oral solution contains oxycodone, a Schedule II controlled substance. As an opioid, oxycodone hydrochloride and acetaminophen oral solution exposes users to the risks of addiction, abuse, and misuse [see **DRUG ABUSE AND DEPENDENCE**]. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxycodone hydrochloride and acetaminophen oral solution. 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 hydrochloride and acetaminophen oral solution, and monitor all patients receiving oxycodone hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution, but use in such patients necessitates intensive counseling about the risks and proper use of oxycodone hydrochloride and acetaminophen oral solution along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescriptive alternatives 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 hydrochloride and acetaminophen oral solution. 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 a 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/OpioidAnalgesicREMS/PCG](http://www.fda.gov/OpioidAnalgesicREMS/PCG).
- 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.opioidanalgesicrems.com](http://www.opioidanalgesicrems.com). The FDA Blueprint can be found at [www.fda.gov/OpioidAnalgesicREMS/Blueprint](http://www.fda.gov/OpioidAnalgesicREMS/Blueprint).

#### 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 hydrochloride and acetaminophen oral solution, 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 hydrochloride and acetaminophen oral solution.

To reduce the risk of respiratory depression, proper dosing and titration of oxycodone hydrochloride and acetaminophen oral solution are essential [see **DOSAGE AND ADMINISTRATION**]. Overestimating the oxycodone hydrochloride and acetaminophen oral solution dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of oxycodone hydrochloride and acetaminophen oral solution, especially by children, can result in respiratory depression and death due to an overdose of oxycodone hydrochloride and acetaminophen oral solution.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see **PRECAUTIONS, Information for Patients/Caregivers**].

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoexia. 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 hydrochloride and acetaminophen oral solution. 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: Addition, 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 hydrochloride and acetaminophen oral solution 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 From Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

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

Concomitant use of oxycodone hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

**Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients**
The use of oxycodone hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution-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 hydrochloride and acetaminophen oral solution [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 hydrochloride and acetaminophen oral solution and when oxycodone hydrochloride and acetaminophen oral solution is 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



### The possible side effects of Prolate:

- 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 Prolate. 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.**

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#### Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in oxycodone hydrochloride and acetaminophen oral solution. Advise patients how to recognize such a reaction and when to seek medical attention [see **CONTRAINDICATIONS, ADVERSE REACTIONS**].

#### Pregnancy

##### *Neonatal Opioid Withdrawal Syndrome*

Inform female patients of reproductive potential that prolonged use of oxycodone hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution can cause fetal harm and to avoid healthcare provider 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**].

#### Fertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see **ADVERSE REACTIONS**].

#### Driving or Operating Heavy Machinery

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

#### Constitution

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

#### 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 methoximinomethylsilyl (MO-TMS) derivative.

#### Drug Interactions

##### *Inhibitors of CYP3A4 and CYP2D6*

The concomitant use of oxycodone hydrochloride and acetaminophen oral solution 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, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of oxycodone hydrochloride and acetaminophen oral solution and CYP3A4 and CYP2D6 inhibitors, particularly when an inhibitor is added after a stable dose of oxycodone hydrochloride and acetaminophen oral solution is achieved [see **WARNINGS**].

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will increase [see **CLINICAL PHARMACOLOGY**], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone hydrochloride and acetaminophen oral solution.

If concomitant use is necessary, consider dosage reduction of oxycodone hydrochloride and acetaminophen oral solution 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 hydrochloride and acetaminophen oral solution dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

##### *Inducers of CYP3A4*

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

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase [see **CLINICAL PHARMACOLOGY**], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

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

#### Benzodiazepines and Other CNS Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines and other CNS depressants such as benzodiazepines and other sedative hypnotics, anxiolytics, and tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, including alcohol, can increase the risk of hypotension, 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. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [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), tryptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and monoamine oxidase (MAO) inhibitors used to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome [see **PRECAUTIONS; Information for Patients/Caregivers**].

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

#### Monoamine Oxidase Inhibitors (MAOIs)

The concomitant use of opioids and MAOIs, such as phelzinate, tranylcypromine, linezolid, may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see **WARNINGS**].

The use of oxycodone hydrochloride and acetaminophen oral solution is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

#### Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

The concomitant use of opioids with other opioid analgesics, such as buprenorphine, nalbuphine, pentazocine, may reduce the analgesic effect of oxycodone hydrochloride and acetaminophen oral solution and/or precipitate withdrawal symptoms.

Advise patient to avoid concomitant use of these drugs.

#### Muscle Relaxants

Oxycodone hydrochloride and acetaminophen oral solution may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increase in the degree of respiratory depression.

If concomitant use is warranted, monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of oxycodone hydrochloride and acetaminophen oral solution and/or the muscle relaxant as necessary. Due to the risk of respiratory depression, concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose [see **WARNINGS**].

#### Diuretics

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

If concomitant use is warranted, monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

#### Anticholinergic Drugs

The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

If concomitant use is warranted, monitor patients for signs of urinary retention or reduced gastric motility when oxycodone hydrochloride and acetaminophen oral solution is used concomitantly with anticholinergic drugs.

#### Alcohol, ethyl

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

#### 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 (Propranolol)

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 hydrochloride and acetaminophen oral solution 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 human 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*

Long-term studies to evaluate the carcinogenic potential of the combination of oxycodone hydrochloride and acetaminophen have not been conducted.

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 8000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 0.7 times or mice at up to 1.2-1.4 times the MHDD, based on a body surface area comparison.

##### *Mutagenesis*

The combination of oxycodone hydrochloride and acetaminophen has not been evaluated for mutagenicity. Oxycodone alone was negative in a bacterial reverse mutation assay (Ames) and *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.

In the published literature, acetaminophen has been reported to be clastogenic when administered at 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

##### *Impairment of Fertility*

In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.78 times the MHDD (based on a body surface comparison) and there was a reduction in the number of mating pairs producing a litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

##### *Fertility*

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 hydrochloride and acetaminophen oral solution. It is also not known whether oxycodone hydrochloride and acetaminophen oral solution can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Oxycodone hydrochloride and acetaminophen oral solution 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 or 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 hydrochloride and acetaminophen oral solution is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including oxycodone hydrochloride and acetaminophen oral solution, 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

Ordinarily, nursing should not be undertaken while a patient is receiving oxycodone hydrochloride and acetaminophen oral solution because of the possibility of sedation and/or respiratory depression in the infant. Oxycodone is excreted in breast milk in low concentrations, and there have been rare reports of somnolence and lethargy in babies of nursing mothers taking an opioid/acetaminophen product. Acetaminophen is also excreted in breast milk in low concentrations.

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

Infants exposed to oxycodone hydrochloride and acetaminophen oral solution 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 of oxycodone hydrochloride and acetaminophen oral solution in pediatric patients have not been established.

#### Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to oxycodone hydrochloride and acetaminophen oral solution. 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 hydrochloride and acetaminophen oral solution slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see **WARNINGS**].

These drugs are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

#### Hepatic Impairment

In a pharmacokinetic study of oxycodone in patients with end-stage liver disease, oxycodone plasma clearance decreased and the elimination half-life increased.

Because oxycodone is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Initiate therapy in these patients with a lower than usual dosage of oxycodone hydrochloride and acetaminophen oral solution and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see **CLINICAL PHARMACOLOGY**].

#### 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.

Because oxycodone is known to be substantially excreted by the kidney, its clearance may decrease in patients with renal impairment. Initiate therapy with a lower than usual dosage of oxycodone hydrochloride and acetaminophen oral solution and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see **CLINICAL PHARMACOLOGY**].

#### ADVERSE REACTIONS

The following adverse reactions have been identified during post approval use of oxycodone hydrochloride and acetaminophen oral solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious adverse reactions that may be associated with oxycodone hydrochloride and acetaminophen oral solution use include respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and shock [see **OVERDOSAGE**].

The most frequently observed non-serious adverse reactions include lightheadedness, dizziness, somnolence 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 have likewise been associated with acetaminophen oral solution. 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 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, central 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, prostaticria, renal insufficiency and failure, urinary retention

- Serotonin Syndrome:* Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
- Adrenal insufficiency:* Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- Anaphylaxis:* Anaphylaxis has been reported with ingredients contained in oxycodone hydrochloride and acetaminophen oral solution.
- Androgen deficiency:* Cases of androgen deficiency have occurred with chronic use of opioids [see **CLINICAL PHARMACOLOGY**].

#### DRUG ABUSE AND DEPENDENCE

##### *Controlled Substance*

Oxycodone hydrochloride and acetaminophen oral solution contains oxycodone, a Schedule II controlled substance.

##### *Abuse*

Oxycodone hydrochloride and acetaminophen oral solution contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and tapentadol. Oxycodone hydrochloride and acetaminophen oral solution can be abused and is 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 reawarding 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 hydrochloride and acetaminophen oral solution, 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 Hydrochloride and Acetaminophen Oral Solution*

Oxycodone hydrochloride and acetaminophen oral solution is for oral use only. Abuse of oxycodone hydrochloride and acetaminophen oral solution poses a risk of overdose and death. The risk is increased with concurrent abuse of oxycodone hydrochloride and acetaminophen oral solution with alcohol and other central nervous system depressants.

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death.

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

#### Dependence

Both tolerance and physical dependence can develop during 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 is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting 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 (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

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

When discontinuing oxycodone hydrochloride and acetaminophen oral solution, gradually taper the dosage using a patient-specific pain plan that considers the following: the dose of oxycodone hydrochloride and acetaminophen oral solution the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [see **DOSE AND ADMINISTRATION, WARNINGS**].

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

#### OVERDOSAGE

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