

**OXYCODONE HYDROCHLORIDE AND IBUPROFEN- oxycodone hydrochloride and  
ibuprofen tablet, film coated**  
**Actavis Pharma, Inc.**

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**Oxycodone Hydrochloride and Ibuprofen Tablets**

**CII**

**Rx Only**

**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; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; and SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

### **Addiction, Abuse, and Misuse**

Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets. Monitor for respiratory depression, especially during initiation of Oxycodone Hydrochloride and Ibuprofen Tablets or following a dose increase [see WARNINGS].

### **Accidental Ingestion**

Accidental ingestion of Oxycodone Hydrochloride and Ibuprofen Tablets, especially by children, can result in a fatal overdose of Oxycodone Hydrochloride and Ibuprofen Tablets [see WARNINGS].

### **Neonatal Opioid Withdrawal Syndrome**

Prolonged use of Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets and any CYP3A4 inhibitor or inducer [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

### **Risk 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 Ibuprofen 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.

### **Cardiovascular Thrombotic Events**

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [see **WARNINGS**].
- Oxycodone Hydrochloride and Ibuprofen Tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see **CONTRAINDICATIONS, WARNINGS**].

### **Gastrointestinal Bleeding, Ulceration, and Perforation**

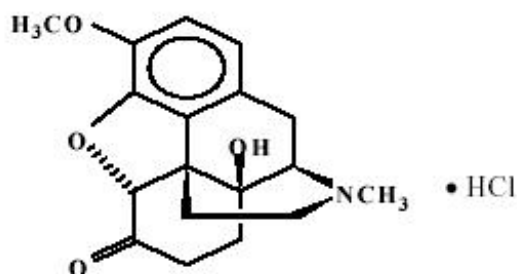
NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [see **WARNINGS**].

## **DESCRIPTION**

Each Oxycodone Hydrochloride and Ibuprofen Tablets contain: Oxycodone hydrochloride, USP 5 mg and Ibuprofen, USP 400 mg.

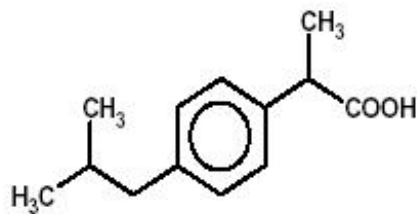
Oxycodone Hydrochloride and Ibuprofen Tablets are supplied in a fixed combination tablet form for oral administration and combines the opioid analgesic agent, oxycodone hydrochloride, with the nonsteroidal anti-inflammatory (NSAID) agent, ibuprofen.

Oxycodone hydrochloride, USP is a centrally acting semisynthetic opioid analgesic. Its chemical name is 4,5 $\alpha$ - Epoxy-14-hydroxy-3-methoxy-methylmorphinan-6-one hydrochloride. Its molecular formula is C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub> •HCl and molecular weight is 351.82. Its structural formula is:



Ibuprofen, USP is a nonsteroidal anti-inflammatory agent [non-selective COX inhibitor] with analgesic and antipyretic properties. Its chemical name is (±)-2-(p-isobutylphenyl) propionic acid. Its molecular

formula is  $C_{13}H_{18}O_2$  and molecular weight is 206.29. Its structural formula is:



Inactive ingredients in Oxycodone Hydrochloride and Ibuprofen Tablets include: calcium stearate, croscarmellose sodium, colloidal silicon dioxide, hydroxypropyl cellulose, microcrystalline cellulose, pregelatinized starch (corn), and stearic acid. The coloring agents consist of hypromellose, lactose monohydrate, polyethylene glycol, synthetic yellow iron oxide, titanium dioxide, and triacetin.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

#### Oxycodone hydrochloride component

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.

#### Ibuprofen component

Ibuprofen has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action, like that of other NSAIDs, is not completely understood, but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Ibuprofen is a potent inhibitor of prostaglandin synthesis *in vitro*. Ibuprofen concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because ibuprofen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

### 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.

#### 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**].

In a healthy volunteer study, ibuprofen 400 mg given once daily, administered 2 hours prior to immediate-release aspirin (81 mg) for 6 days, showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B<sub>2</sub> (Tx<sub>B2</sub>) inhibition at 24 hours following the day-6 aspirin dose [53%]. An interaction was still observed, but minimized, when ibuprofen 400 mg given once-daily was administered as early as 8 hours prior to the immediate-release aspirin dose [90.7%]. However, there was no interaction with the antiplatelet activity of aspirin when ibuprofen 400 mg, given once daily, was administered 2 hours after (but not concomitantly, 15 min, or 30 min after) the immediate-release aspirin dose [99.2%].

In another study, where immediate-release aspirin 81 mg was administered once daily with ibuprofen 400 mg given three times daily (1, 7, and 13 hours post-aspirin dose) for 10 consecutive days, the mean % serum thromboxane B<sub>2</sub> (Tx<sub>B2</sub>) inhibition suggested no interaction with the antiplatelet activity of aspirin [98.3%]. However, there were individual subjects with serum Tx<sub>B2</sub> inhibition below 95%, with the lowest being 90.2%.

When a similarly designed study was conducted with enteric-coated aspirin, where healthy subjects were administered enteric-coated aspirin 81 mg once daily for 6 days and ibuprofen 400 mg three times

daily (2, 7 and 12 h post-aspirin dose) for 6 days, there was an interaction with the antiplatelet activity at 24 hours following the day-6 aspirin dose [67%]. [see **PRECAUTIONS; Drug Interactions**].

## **Pharmacokinetics**

### Absorption

Oxycodone is rapidly absorbed after single dose administration of Oxycodone Hydrochloride and Ibuprofen Tablets. Maximum concentrations ( $C_{max}$ ) of oxycodone, ranging from 9.8 ng/mL to 11.7 ng/mL, are obtained within 1.3 hr to 2.1 hr after administration of oxycodone hydrochloride and ibuprofen. Repeated administration of oxycodone hydrochloride and ibuprofen, every 6 hours, results in approximately 50% to 65% increase in  $C_{max}$ . In the presence of food, the bioavailability of oxycodone is slightly (25%) increased.

Ibuprofen is rapidly absorbed after oral administration of Oxycodone Hydrochloride and Ibuprofen Tablets.  $C_{max}$  values range from 18.5 mcg/mL to 34.3 mcg/mL and are reached 1.6 hr to 3.1 hr after oral administration of oxycodone hydrochloride and ibuprofen. Repeated administration of oxycodone hydrochloride and ibuprofen every 6 hours does not result in any accumulation of ibuprofen. The bioavailability of ibuprofen is not altered in the presence of food.

### Distribution

Oxycodone binding to protein in serum is approximately 45%.

Ibuprofen is extensively bound to plasma proteins (99%).

### Metabolism

#### **Oxycodone**

A high portion of oxycodone is N-dealkylated to noroxycodone during first-pass metabolism, and is catalyzed by CYP3A4. Oxymorphone is formed by the O-demethylation of oxycodone. The metabolism of oxycodone to oxymorphone is catalyzed by CYP2D6. Free and conjugated noroxycodone, free and conjugated oxycodone, and oxymorphone are excreted in human urine following a single oral dose of oxycodone. Approximately 8% to 14% of the dose is excreted as free oxycodone over 24 hours after administration. Following a single, oral dose of oxycodone, the mean  $\pm$  SD elimination half-life is 3.51  $\pm$  1.43 hours.

#### **Ibuprofen**

Ibuprofen is present as a racemate and following absorption, it undergoes interconversion in the plasma from the R-isomer to the S-isomer.

Both the R- and S-isomers are metabolized to two primary metabolites: (+)-2-4'-(2-hydroxy-2-methylpropyl) phenyl propionic acid and (+)-2-4'-(2-carboxypropyl) phenyl propionic acid, both of which circulate in the plasma at low levels relative to the parent.

### Elimination

Oxycodone is eliminated from the systemic circulation with half-life ( $T_{1/2}$ ) values ranging from 3.1 hr to 3.7 hr after single dose administration of Oxycodone Hydrochloride and Ibuprofen Tablets. Urinary excretion of unchanged oxycodone amounts to approximately 4% of the administered oxycodone dose.

Ibuprofen is eliminated from the systemic circulation with half-life ( $T_{1/2}$ ) values ranging from 1.8 hr to 2.6 hr after single dose administration of Oxycodone Hydrochloride and Ibuprofen Tablets. Urinary excretion of unchanged ibuprofen is minimal (less than 0.2% of administered ibuprofen dose).

### Special Populations

**Gender:** There are no gender effects on the pharmacokinetics of oxycodone or ibuprofen after administration of Oxycodone Hydrochloride and Ibuprofen Tablets.

**Age:** The effects of age on the pharmacokinetics of oxycodone and ibuprofen after administration of Oxycodone Hydrochloride and Ibuprofen Tablets have not been evaluated.

When either drug was administered alone, the pharmacokinetics of oxycodone and ibuprofen were similar in elderly subjects, compared to young healthy subjects.

*Pediatrics:* The pharmacokinetics of oxycodone and ibuprofen after administration of Oxycodone Hydrochloride and Ibuprofen Tablets has not been evaluated in a pediatric population.

*Renal Impairment:* The effects of renal impairment on the pharmacokinetics of oxycodone and ibuprofen after administration of Oxycodone Hydrochloride and Ibuprofen Tablets have not been evaluated [see **PRECAUTIONS; Renal Impairment**].

*Hepatic Impairment:* The effects of hepatic impairment on the pharmacokinetics of oxycodone and ibuprofen after administration of Oxycodone Hydrochloride and Ibuprofen Tablets have not been evaluated [see **PRECAUTIONS; Hepatic Impairment**].

#### Drug Interaction Studies

*Aspirin:* When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known [see **PRECAUTIONS; Drug Interactions**].

## CLINICAL STUDIES

Oxycodone hydrochloride and ibuprofen combination product was investigated in three clinical studies. Two studies involving a total of 949 patients following dental surgery (removal of ipsilateral molars) and a third study of 456 patients following abdominal/pelvic surgery were conducted. In the three studies patients were administered a single dose of the Oxycodone Hydrochloride and Ibuprofen Tablets, ibuprofen alone, oxycodone hydrochloride alone or placebo for acute, moderate to severe pain.

In these single dose studies, oxycodone hydrochloride and ibuprofen combination product produced greater efficacy than placebo and each of Oxycodone Hydrochloride and Ibuprofen Tablets individual components as measured by the magnitude of pain relief and the reduction in pain intensity through six hours. No multiple dose efficacy studies have been performed with oxycodone hydrochloride and ibuprofen.

## INDICATIONS AND USAGE

Oxycodone Hydrochloride and Ibuprofen Tablets are indicated for the management of short term (no more than 7 days) acute to moderate pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

#### Limitations of Use

Carefully consider the potential benefits and risks of Oxycodone Hydrochloride and Ibuprofen Tablets and other treatment options before deciding to use Oxycodone Hydrochloride and Ibuprofen Tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [see **WARNINGS; Cardiovascular Thrombotic Events, and Gastrointestinal Bleeding, Ulceration, and Perforation**].

Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see **WARNINGS; Addiction, Abuse, and Misuse**], reserve Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets are contraindicated in patients with:

- Significant respiratory depression [see **WARNINGS; Life-Threatening Respiratory Depression**].
- Acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment [see **WARNINGS; Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients**].
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see **WARNINGS; Risks of Use in Patients with Gastrointestinal Conditions**].
- Known hypersensitivity to oxycodone, ibuprofen, or any components in Oxycodone Hydrochloride and Ibuprofen Tablets [see **WARNINGS; Anaphylactic reactions, Serious skin reactions**].
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [see **WARNINGS; Anaphylactic Reactions, Exacerbation of Asthma Related to Aspirin Sensitivity**].
- In the setting of coronary artery bypass graft (CABG) surgery [see **WARNINGS; Cardiovascular Thrombotic Events**].

## WARNINGS

### Oxycodone component

#### Addiction, Abuse, and Misuse

Oxycodone Hydrochloride and Ibuprofen Tablets contain oxycodone, a Schedule II controlled substance. As an opioid containing product, Oxycodone Hydrochloride and Ibuprofen Tablets expose users to the risks of addiction, abuse, and misuse [see **DRUG ABUSE AND DEPENDENCE**].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets, and monitor all patients receiving Oxycodone Hydrochloride and Ibuprofen 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-containing products such as Oxycodone Hydrochloride and Ibuprofen Tablets, but use in such patients necessitates intensive counseling about the risks and proper use of Oxycodone Hydrochloride and Ibuprofen Tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Oxycodone Hydrochloride and Ibuprofen Tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see **PRECAUTIONS; Information for Patients**]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

#### 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/OpioidAnalgesicREMSPCG](http://www.fda.gov/OpioidAnalgesicREMSPCG).
- 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/OpioidAnalgesicREMSBlueprint](http://www.fda.gov/OpioidAnalgesicREMSBlueprint).

### **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 Ibuprofen 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 Hydrochloride and Ibuprofen Tablets.

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

Accidental ingestion of Oxycodone Hydrochloride and Ibuprofen Tablets, especially by children, can result in respiratory depression and death due to an overdose of Oxycodone Hydrochloride and Ibuprofen Tablets.

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**].

### **Neonatal Opioid Withdrawal Syndrome**

Prolonged use of Oxycodone Hydrochloride and Ibuprofen 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, Pregnancy**].

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

Concomitant use of Oxycodone Hydrochloride and Ibuprofen 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**;

***Life Threatening Respiratory Depression***], particularly when an inhibitor is added after a stable dose of Oxycodone Hydrochloride and Ibuprofen Tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in oxycodone hydrochloride and ibuprofen-treated patients may increase oxycodone hydrochloride plasma concentrations and prolong opioid adverse reactions. When using Oxycodone Hydrochloride and Ibuprofen Tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in oxycodone hydrochloride and ibuprofen-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Oxycodone Hydrochloride and Ibuprofen Tablets until stable drug effects are achieved [*see DOSAGE AND ADMINISTRATION, PRECAUTIONS; Drug Interactions*].

Concomitant use of Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [*see PRECAUTIONS; Drug Interactions*].

### **Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [*see PRECAUTIONS; Drug Interactions*].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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

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

The use of Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets and when Oxycodone Hydrochloride and Ibuprofen 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 1 month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

### **Severe Hypotension**

Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets. In patients with circulatory shock, Oxycodone Hydrochloride and Ibuprofen Tablets may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of Oxycodone Hydrochloride and Ibuprofen Tablets with circulatory shock.

### **Risk 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 Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Oxycodone Hydrochloride and Ibuprofen Tablets in patients with impaired consciousness or coma.

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

Oxycodone Hydrochloride and Ibuprofen Tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The administration of Oxycodone Hydrochloride and Ibuprofen Tablets or other opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

The oxycodone in Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets therapy.

### **Withdrawal**

Do not abruptly discontinue Oxycodone Hydrochloride and Ibuprofen Tablets in a patient physically dependent on opioids. Rapid tapering of Oxycodone Hydrochloride and Ibuprofen 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*].

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including Oxycodone Hydrochloride and Ibuprofen Tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing Oxycodone Hydrochloride and Ibuprofen Tablets, gradually taper the dosage [*see DOSAGE AND ADMINISTRATION*]. Do not abruptly discontinue Oxycodone Hydrochloride and Ibuprofen Tablets [*see DRUG ABUSE AND DEPENDENCE*].

### **Ibuprofen Component**

#### **Cardiovascular Thrombotic Events**

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ibuprofen tablets, increases the risk of serious gastrointestinal (GI) events [*see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see CONTRAINDICATIONS*].

### Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of Oxycodone Hydrochloride and Ibuprofen Tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Oxycodone Hydrochloride and Ibuprofen Tablets are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

### **Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation**

NSAIDs, including ibuprofen, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. However, even short-term therapy is not without risk.

### Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy, concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking, use of alcohol, older age, and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

### Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For high risk patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue ibuprofen until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see PRECAUTIONS; Drug Interactions*].

### **Hepatotoxicity**

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in

approximately 1% of NSAID-treated patients in clinical trials with NSAIDs. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients taking NSAIDs including ibuprofen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue Oxycodone Hydrochloride and Ibuprofen Tablets immediately, and perform a clinical evaluation of the patient.

### **Hypertension**

NSAID-containing products, including Oxycodone Hydrochloride and Ibuprofen Tablets, can lead to new onset or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazides diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [see **PRECAUTIONS; Drug Interactions**].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

### **Heart Failure and Edema**

The Coxib and traditional NSAID Trialists’ Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of Oxycodone Hydrochloride and Ibuprofen Tablets may blunt the CV effects of several therapeutic agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)] [see **PRECAUTIONS; Drug Interactions**].

Avoid the use of Oxycodone Hydrochloride and Ibuprofen Tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If Oxycodone Hydrochloride and Ibuprofen Tablets are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

### **Renal Toxicity and Hyperkalemia**

#### Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or Angiotensin II Receptor Blockers (ARBs), and the elderly. Discontinuation of NSAID therapy was usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of Oxycodone Hydrochloride and Ibuprofen Tablets in patients with advanced renal disease. The renal effects of Oxycodone Hydrochloride and Ibuprofen Tablets may hasten the progression of renal dysfunction in

patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating Oxycodone Hydrochloride and Ibuprofen Tablets. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Oxycodone Hydrochloride and Ibuprofen Tablets [see **PRECAUTIONS; Drug Interactions**]. Avoid the use of Oxycodone Hydrochloride and Ibuprofen Tablets in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Oxycodone Hydrochloride and Ibuprofen Tablets are used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

### Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

### **Anaphylactic Reactions**

Ibuprofen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to ibuprofen and in patients with aspirin-sensitive asthma [see **CONTRAINDICATIONS, PRECAUTIONS; Exacerbation of Asthma Related to Aspirin Sensitivity**].

Seek emergency help if an anaphylactic reaction occurs.

### **Exacerbation of Asthma Related to Aspirin Sensitivity**

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, Oxycodone Hydrochloride and Ibuprofen Tablets are contraindicated in patients with this form of aspirin sensitivity [see **CONTRAINDICATIONS**]. When Oxycodone Hydrochloride and Ibuprofen Tablets are used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

### **Serious Skin Reactions**

NSAIDs, including ibuprofen, can cause serious skin adverse events such as exfoliative dermatitis, Stevens- Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of Oxycodone Hydrochloride and Ibuprofen Tablets at the first appearance of skin rash or any other sign of hypersensitivity. Oxycodone Hydrochloride and Ibuprofen Tablets are contraindicated in patients with previous serious skin reactions to NSAIDs [see **CONTRAINDICATIONS**].

### **Premature Closure of Fetal Ductus Arteriosus**

Ibuprofen may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Oxycodone Hydrochloride and Ibuprofen Tablets, in pregnant women starting at 30 weeks of gestation (third trimester) [see **PRECAUTIONS; Pregnancy**].

### **Hematologic Toxicity**

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with Oxycodone Hydrochloride and Ibuprofen Tablets, has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAID-containing products, including Oxycodone Hydrochloride and Ibuprofen Tablets, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [see **PRECAUTIONS; Drug Interactions**].

### **Aseptic Meningitis**

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen as found in Oxycodone Hydrochloride and Ibuprofen Tablets. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on Oxycodone Hydrochloride and Ibuprofen Tablets, the possibility of its being related to ibuprofen should be considered.

## **PRECAUTIONS**

### **Risks of Driving and Operating Machinery**

Oxycodone Hydrochloride and Ibuprofen Tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Oxycodone Hydrochloride and Ibuprofen Tablets and know how they will react to the medication [see **PRECAUTIONS; Information for Patients**].

### **General**

Oxycodone Hydrochloride and Ibuprofen Tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

### **Masking of Inflammation and Fever**

The pharmacological activity of Oxycodone Hydrochloride and Ibuprofen Tablets in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

### **Ophthalmological Effects**

Blurred or diminished vision, scotomata, and changes in color vision have been reported with oral ibuprofen.

Discontinue ibuprofen if a patient develops such complaints, and refer the patient for an ophthalmologic examination that includes central visual fields and color vision testing.

### **Information for Patients**

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

### **Storage and Disposal**

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store Oxycodone Hydrochloride and Ibuprofen Tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home [see **WARNINGS, DRUG ABUSE AND DEPENDENCE**]. Inform patients that leaving Oxycodone Hydrochloride and Ibuprofen Tablets unsecured can pose a deadly risk to others in the home.



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

#### Addiction, Abuse, and Misuse

Inform patients that the use of Oxycodone Hydrochloride and Ibuprofen Tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see **WARNINGS; Addiction, Abuse, and Misuse**]. Instruct patients not to share Oxycodone Hydrochloride and Ibuprofen Tablets with others and to take steps to protect Oxycodone Hydrochloride and Ibuprofen Tablets from theft or misuse.

#### Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting Oxycodone Hydrochloride and Ibuprofen Tablets or when the dosage is increased, and that it can occur even at recommended dosages [see **WARNINGS; Life-Threatening Respiratory Depression**]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

#### Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see **WARNINGS; Life-Threatening Respiratory Depression**]. Instruct patients to take steps to store Oxycodone Hydrochloride and Ibuprofen Tablets securely and to dispose of unused Oxycodone Hydrochloride and Ibuprofen Tablets by flushing the unused tablets down the toilet when they are no longer needed.

#### Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if Oxycodone Hydrochloride and Ibuprofen Tablets are used with benzodiazepines and other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see **WARNINGS; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants, PRECAUTIONS; Drug Interactions**].

#### Serotonin Syndrome

Inform patients that Oxycodone Hydrochloride and Ibuprofen Tablets opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications [see **PRECAUTIONS; Drug Interactions**].

#### Monoamine Oxidase Inhibitor (MAOI) Interaction

Inform patients to avoid taking Oxycodone Hydrochloride and Ibuprofen Tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking Oxycodone Hydrochloride and Ibuprofen Tablets [see **PRECAUTIONS; Drug Interactions**].

#### Adrenal Insufficiency

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

### Important Administration Instructions

Instruct patients how to properly take Oxycodone Hydrochloride and Ibuprofen Tablets. For the short-term (less than 7 days) management of pain, the recommended dose of Oxycodone Hydrochloride and Ibuprofen Tablets is one tablet every 6 hours, as necessary. Inform patients that the dosage should not exceed 4 tablets in a 24-hour period [see **DOSAGE AND ADMINISTRATION, WARNINGS, PRECAUTIONS**].

### Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue Oxycodone Hydrochloride and Ibuprofen Tablets without first discussing a tapering plan with the prescriber [see **DOSAGE AND ADMINISTRATION**]

### Hypotension

Inform patients that Oxycodone Hydrochloride and Ibuprofen Tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see **WARNINGS; Severe Hypotension**].

### Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in Oxycodone Hydrochloride and Ibuprofen Tablets. Inform 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 Ibuprofen Tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see **WARNINGS, PRECAUTIONS; Pregnancy**].

#### *Embryo-Fetal Toxicity*

Inform pregnant women to avoid use of Oxycodone Hydrochloride and Ibuprofen Tablets and other NSAIDs starting at 30 weeks gestation because of the risk of premature closing of the fetal ductus arteriosus [see **WARNINGS; Premature Closure of Fetal Ductus Arteriosus, PRECAUTIONS; Pregnancy**].

Inform female patients of reproductive potential that Oxycodone Hydrochloride and Ibuprofen Tablets can cause fetal harm and to inform the healthcare provider of a known or suspected 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**].

### Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see **PRECAUTIONS; Carcinogenesis, Mutagenesis, Impairment of Fertility**].

### Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including Oxycodone Hydrochloride and Ibuprofen Tablets, may be associated with a reversible delay in ovulation [see **PRECAUTIONS; Carcinogenesis, Mutagenesis, Impairment of Fertility**].

### Driving or Operating Heavy Machinery

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

### Constipation

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

### Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see **WARNINGS; Cardiovascular Thrombotic Events**].

### Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for the signs and symptoms of GI bleeding [see **WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation**].

### Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop Oxycodone Hydrochloride and Ibuprofen Tablets and seek immediate medical therapy [see **WARNINGS; Hepatotoxicity**].

### Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see **WARNINGS; Heart Failure and Edema**].

### Serious Skin Reactions

Advise patients to stop Oxycodone Hydrochloride and Ibuprofen Tablets immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see **WARNINGS; Serious Skin Reactions**].

### Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see **WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation, PRECAUTIONS; Drug Interactions**]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

### Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with Oxycodone Hydrochloride and Ibuprofen Tablets until they talk to their healthcare provider [see **PRECAUTIONS; Drug Interactions**].

### **Laboratory Monitoring**

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [see **WARNINGS; Gastrointestinal Bleeding, Ulceration and Perforation, Renal Toxicity and Hyperkalemia, and Hepatotoxicity**].

### **Drug Interactions**

### Inhibitors of CYP3A4 and CYP2D6

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

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone hydrochloride and ibuprofen plasma concentration will decrease [see **CLINICAL PHARMACOLOGY**], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to Oxycodone Hydrochloride and Ibuprofen Tablets.

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

### Inducers of CYP3A4

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

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone hydrochloride 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 Ibuprofen Tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider Oxycodone Hydrochloride and Ibuprofen Tablets dosage reduction and monitor for signs of respiratory depression.

### Benzodiazepines and Other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as benzodiazepines and other sedatives/hypnotics, anxiolytics, 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 [see **WARNINGS**].

### Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> 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 (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome [see **PRECAUTIONS; Information for Patients**].

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Oxycodone Hydrochloride and Ibuprofen Tablets if serotonin syndrome is suspected.

#### Monoamine Oxidase Inhibitors (MAOIs)

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

The use of Oxycodone Hydrochloride and Ibuprofen Tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

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

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

Agonist/antagonist analgesics such as pentazocine, nalbuphine, butorphanol and buprenorphine may reduce the analgesic effect of Oxycodone Hydrochloride and Ibuprofen Tablets and/or precipitate withdrawal symptoms in these patients.

Avoid concomitant use of these drugs.

#### Muscle Relaxants

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

Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Oxycodone Hydrochloride and Ibuprofen Tablets and/or the muscle relaxant as necessary.

#### Anticholinergics

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

Monitor patients for signs of urinary retention or reduced gastric motility when Oxycodone Hydrochloride and Ibuprofen Tablets are used concomitantly with anticholinergic drugs.

#### Neuromuscular Blocking Agents

Oxycodone, as well as other opioid analgesics, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

#### Drugs That Interfere With Hemostasis

Ibuprofen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of ibuprofen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone.

Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.

Monitor patients with concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding [see **PRECAUTIONS; Hematologic Toxicity**].

#### Aspirin

Pharmacodynamic studies have demonstrated interference with the antiplatelet activity of aspirin when ibuprofen 400 mg, given three times daily, is administered with enteric-coated low-dose aspirin. The

interaction exists even following a once-daily regimen of ibuprofen 400 mg, particularly when ibuprofen is dosed prior to aspirin. The interaction is alleviated if immediate-release low-dose aspirin is dosed at least 2 hours prior to a once-daily regimen of ibuprofen; however, this finding cannot be extended to enteric-coated low-dose aspirin [see **CLINICAL PHARMACOLOGY; Pharmacodynamics**].

Because there may be an increased risk of cardiovascular events due to the interference of ibuprofen with the antiplatelet effect of aspirin, for patients taking low-dose aspirin for cardioprotection who require analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics, where appropriate.

Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [see **WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation**].

Concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [see **PRECAUTIONS; Hematologic Toxicity**].

#### ACE-Inhibitors, Angiotensin Receptor Blockers, and Beta-blockers

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).

During concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

During concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and ACE-inhibitors, ARBs, or beta-blockers, in who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [see **WARNINGS; Renal Toxicity and Hyperkalemia**].

When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.

#### Diuretics

Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.

During concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see **WARNINGS; Renal Toxicity and Hyperkalemia**].

#### Digoxin

The concomitant use of ibuprofen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.

During concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and digoxin, monitor serum digoxin levels.

#### Lithium

NSAIDs have produced elevations in plasma lithium concentration and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was

decreased by approximately 20%. This effect has been attributed to inhibition of renal prostaglandin synthesis.

During concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and lithium, monitor patients for signs of lithium toxicity.

#### Methotrexate

Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).

During concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and methotrexate, monitor patients for methotrexate toxicity.

#### Cyclosporine

Concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and cyclosporine may increase cyclosporine's nephrotoxicity.

During concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and cyclosporine, monitor patients for signs of worsening renal function.

#### NSAIDs and Salicylates

Concomitant use of ibuprofen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [see **WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation**].

The concomitant use of ibuprofen with other NSAIDs or salicylates is not recommended.

#### Pemetrexed

Concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).

During concomitant use of Oxycodone Hydrochloride and Ibuprofen Tablets and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity.

NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed.

In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

Studies to evaluate the potential effects of oxycodone, ibuprofen, or the combination of oxycodone and ibuprofen on carcinogenicity and mutagenicity have not been conducted.

#### Mutagenesis

Oxycodone hydrochloride was not genotoxic in the following assays: Ames bacterial mutation assay, chromosomal aberrations in cultured human lymphocytes, and *in vivo* mouse micronucleus assay in mice. In published studies, ibuprofen was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames assay).

#### Impairment of Fertility

There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered oxycodone hydrochloride; ibuprofen up to (1:80 mg/kg/day) which is equivalent to 0.5-

times the maximum recommended human daily dose (MRHD) (20:1600 mg/day) on a body surface area (mg/m<sup>2</sup>) basis.

In a published study, dietary administration of ibuprofen to male and female rats 8-weeks prior to and during mating at dose levels of 20 mg/kg (0.06-times the MRHD based on body surface area comparison) did not impact male or female fertility or litter size.

In other studies, adult mice were administered ibuprofen intraperitoneally at a dose of 5.6 mg/kg/day (0.0085- times the MRHD based on body surface area comparison) for 35 or 60 days in males and 35 days in females. There was no effect on sperm motility or viability in males but decreased ovulation was reported in females.

## **Pregnancy**

### **Teratogenic Effects**

*Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation*

Starting at 30 weeks gestation, Oxycodone Hydrochloride and Ibuprofen Tablets, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. Oxycodone Hydrochloride and Ibuprofen Tablets can cause fetal harm when administered to a pregnant woman starting at 30 weeks gestation. If Oxycodone Hydrochloride and Ibuprofen Tablets, and other NSAIDs, are used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus. There are no adequate and well-controlled studies in pregnant women. Prior to 30 weeks gestation, Oxycodone Hydrochloride and Ibuprofen Tablets should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Animal studies to assess the potential effects of the combination of oxycodone and ibuprofen on embryo-fetal development were conducted in the rat and rabbit model.

Pregnant rats were treated by oral gavage with combination doses of oxycodone:ibuprofen mg/kg/day (0.25:20, 0.5:40, 1:80, or 2:160) on days 7 to 16 of gestation. There was no evidence for developmental toxicity or teratogenicity at any dose, although maternal toxicity was noted at doses of 0.5:40 and above. The highest dose tested in the rat (2:160 mg/kg/day) is equivalent to the maximum recommended human daily dose (20:1600 mg/day) on a body surface area (mg/m<sup>2</sup>) basis. This dose was associated with maternal toxicity (death, clinical signs, decreased BW).

Pregnant rabbits were treated by oral gavage with combination doses of oxycodone:ibuprofen (0.38:30, 0.75:60, 1.5:120 or 3:240 mg/kg/day) on gestation days 7 to 19. Oxycodone:ibuprofen treatment was not teratogenic under the conditions of the assay. Maternal toxicity was noted at doses of 1.5:120 (reduced body weight and food consumption) and 3:240 mg/kg/day (mortality). The NOAEL for maternal toxicity, 0.75:60 mg/kg/day, is 0.75 fold the proposed maximum daily human dose based upon the body surface area. Developmental toxicity, as evidenced by delayed ossification and reduced fetal body weights, was noted at the highest dose, which is approximately 3 times the MRHD on an mg/m<sup>2</sup> basis, and is likely due to maternal toxicity. The fetal no adverse effect level (NOAEL) of 1.50:120 mg/kg/day is approximately 1.5 times the MRHD on an mg/m<sup>2</sup> basis.

In a pre- and post-natal development study conducted in rats, there was increased mortality of pups born to dams dosed with 0.5:40 mg/kg/day oxycodone:ibuprofen and above which is equivalent to 0.25 times of the MRHD (20:1600 mg/day) on a body surface area (mg/m<sup>2</sup>) basis. There was an increase in stillborn F1 pups and decrease in mean pup weight in dams dosed with 1:80 mg/kg/day oxycodone:ibuprofen, which is 0.5 times the MRHD (20:1600 mg/day) on a body surface area (mg/m<sup>2</sup>) basis.

### **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 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 use, 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 Ibuprofen Tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including oxycodone, 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.

Oxycodone Hydrochloride and Ibuprofen Tablets should not be used during the third trimester of pregnancy due to the potential for ibuprofen to inhibit prostaglandin synthetase which may prolong pregnancy and inhibit labor. Oxycodone is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of Oxycodone Hydrochloride and Ibuprofen Tablets on labor and delivery in pregnant women are unknown.

### **Nursing Mothers**

It is not known whether Oxycodone Hydrochloride and Ibuprofen Tablets are excreted in human milk. Oxycodone is excreted in human milk.

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

Infants exposed to oxycodone hydrochloride and ibuprofen 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 breastfeeding is stopped.

### **Pediatric Use**

In the placebo-controlled, clinical studies of pain following dental surgery, 109 patients between the ages of 14 and 17 years were administered a single dose of Oxycodone Hydrochloride and Ibuprofen Tablets. No apparent differences were noted in the safety of oxycodone hydrochloride and ibuprofen in patients below and above 17 years of age. Oxycodone hydrochloride and ibuprofen has not been studied in patients under 14 years of age. Safety and effectiveness in pediatric patients below the age of 14 have not been established.

### **Geriatric Use**

Of the total number of subjects in clinical studies of oxycodone hydrochloride and ibuprofen, 89 patients were 65 and over, while 37 patients were 75 and over. No overall differences in safety were

observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients (aged 65 years or older) may have increased sensitivity to Oxycodone Hydrochloride and Ibuprofen Tablets. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were coadministered with other agents that depress respiration. Titrate the dosage of Oxycodone Hydrochloride and Ibuprofen Tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see **WARNINGS**].

Oxycodone and ibuprofen 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*

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 Ibuprofen Tablets and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see **CLINICAL PHARMACOLOGY**].

#### *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 Ibuprofen Tablets and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see **CLINICAL PHARMACOLOGY**].

## **ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in other sections:

- Addiction, Abuse, and Misuse [see **WARNINGS**]
- Life-Threatening Respiratory Depression [see **WARNINGS**]
- Neonatal Opioid Withdrawal Syndrome [see **WARNINGS**]
- Interactions with Benzodiazepines or Other CNS Depressants [see **WARNINGS**]
- Adrenal Insufficiency [see **WARNINGS**]
- Severe Hypotension [see **WARNINGS**]
- Gastrointestinal Adverse Reactions [see **WARNINGS**]
- Seizures [see **WARNINGS**]
- Withdrawal [see **WARNINGS**]
- Cardiovascular Thrombotic Events [see **WARNINGS**]
- GI Bleeding, Ulceration, and Perforation [see **WARNINGS**]
- Hepatotoxicity [see **WARNINGS**]
- Hypertension [see **WARNINGS**]
- Heart Failure and Edema [see **WARNINGS**]
- Renal Toxicity and Hyperkalemia [see **WARNINGS**]
- Anaphylactic Reactions [see **WARNINGS**]
- Serious Skin Reactions [see **WARNINGS**]
- Hematologic Toxicity [see **WARNINGS**]

## Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Listed below are the adverse event incidence rates from single dose analgesia trials in which a total of 2,437 patients received either oxycodone hydrochloride and ibuprofen combination product, ibuprofen (400 mg), oxycodone hydrochloride (5 mg), or placebo. Adverse event information is also provided from an additional 334 patients who were exposed to oxycodone hydrochloride and ibuprofen combination product in a multiple dose analgesia trial, without placebo or active component comparison arms, given up to four times daily for up to 7 days.

### Adverse Events Which Occurred at a Frequency of $\geq 1\%$ and at a Higher Incidence than in the Placebo Group in Single Dose Studies

	5/400 mg (n=923)	400 mg Ibuprofen (n=913)	5 mg Oxycodone Hydrochloride (n = 286)	Placebo (n=315)
<b>Digestive</b>				
Nausea	81 (8.8%)	44 (4.8%)	46 (16.1%)	21 (6.7%)
Vomiting	49 (5.3%)	16 (1.8%)	30 (10.5%)	10 (3.2%)
Flatulence	9 (1.0%)	7 (0.8%)	3 (1.0%)	0
<b>Nervous System</b>				
Somnolence	67 (7.3%)	38 (4.2%)	12 (4.2%)	7 (2.2%)
Dizziness	47 (5.1%)	21 (2.3%)	17 (5.9%)	8 (2.5%)
<b>Skin and Appendages</b>				
Sweat	15 (1.6%)	7 (0.8%)	4 (1.4%)	1 (0.3%)

Adverse events that were reported by at least 1% of patients taking oxycodone hydrochloride and ibuprofen but were observed at a greater incidence in the placebo treated patients were fever, headache and pruritus.

Adverse events that occurred in less than 1% and in at least two oxycodone hydrochloride and ibuprofen treated patients in **Single Dose** studies not listed above include the following:

**Body as Whole:** abdominal pain, asthenia, chest pain, enlarged abdomen.

**Cardiovascular System:** hypotension, syncope, tachycardia, vasodilation.

**Digestive System:** constipation, dry mouth, dyspepsia, eructation, ileus.

**Hemic and Lymphatic System:** anemia.

**Metabolic and Nutritional Disorders:** edema.

**Nervous System:** euphoria, insomnia, nervousness.

**Respiratory System:** hypoxia, lung disorder, pharyngitis.

**Urogenital System:** urinary retention.

Adverse events that occurred in the **Multiple Dose** study in at least 2% of patients treated with oxycodone hydrochloride and ibuprofen include the following:

**Body as Whole:** asthenia (3.3%), fever (3.0%), headache (10.2%).

**Cardiovascular System:** vasodilation (3.0%).

**Digestive System:** constipation (4.5%), diarrhea (2.1%), dyspepsia (2.1%), nausea (25.4%), vomiting (4.5%).

**Nervous System:** dizziness (19.2%), somnolence (17.4%).

Adverse events that occurred in less than 2% of and at least two oxycodone hydrochloride and ibuprofen treated patients in the **Multiple Dose** study not listed previously include the following:

**Body as Whole:** back pain, chills, infection.

**Cardiovascular System:** thrombophlebitis.

**Hemic and Lymphatic System:** ecchymosis.

**Metabolic and Nutritional Disorders:** hypokalemia.

**Musculoskeletal System:** arthritis.

**Nervous System:** abnormal thinking, anxiety, hyperkinesia, hypertonia.

**Skin and Appendages:** rash.

**Special Senses:** amblyopia, taste perversion.

**Urogenital System:** urinary frequency.

### **Postmarketing Experience**

The following adverse reactions have been identified during post approval use of Oxycodone Hydrochloride and Ibuprofen Tablets. 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.

- **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 Ibuprofen Tablets.
- **Androgen deficiency:** Cases of androgen deficiency have occurred with chronic use of opioids [see **CLINICAL PHARMACOLOGY**].

**To report SUSPECTED ADVERSE EVENTS, contact Actavis at 1-800-432-8534 or FDA at 1-800-FDA-1088 or <http://www.fda.gov/> for voluntary reporting of adverse reactions.**

## **DRUG ABUSE AND DEPENDENCE**

### **Controlled Substance**

Oxycodone Hydrochloride and Ibuprofen Tablets contain oxycodone, a Schedule II controlled substance.

### **Abuse**

Oxycodone Hydrochloride and Ibuprofen Tablets contain oxycodone, a substance with a high potential for abuse similar to other opioids including codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. Oxycodone Hydrochloride and Ibuprofen Tablets can be abused and are subject to misuse, addiction, and criminal diversion [see **WARNINGS; Addiction, Abuse, and Misuse**].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its

rewarding psychological or physiological effects.

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

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

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

Oxycodone Hydrochloride and Ibuprofen Tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

#### Risks Specific to Abuse of Oxycodone Hydrochloride and Ibuprofen Tablets

Oxycodone Hydrochloride and Ibuprofen Tablets are for oral use only. Abuse of Oxycodone Hydrochloride and Ibuprofen Tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of Oxycodone Hydrochloride and Ibuprofen Tablets with alcohol and central nervous system depressants.

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

#### **Dependence**

Both tolerance and physical dependence can develop during 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 Ibuprofen Tablets in a patient physically dependent on opioids. Rapid tapering of Oxycodone Hydrochloride and Ibuprofen Tablets in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing Oxycodone Hydrochloride and Ibuprofen Tablets, gradually taper the dosage using a patient-specific plan that considers the following: the dose of Oxycodone Hydrochloride and

Ibuprofen Tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for 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 **DOSAGE AND ADMINISTRATION, WARNINGS**].

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

## **OVERDOSAGE**

Following an acute overdose, toxicity may result from oxycodone and/or ibuprofen.

### **Clinical Presentation**

#### Oxycodone Component

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

#### Ibuprofen Component

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred [see **WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation**]. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [see **WARNINGS; Hypertension, Renal Toxicity and Hyperkalemia**].

### **Treatment of Overdose**

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

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

Because the duration of opioid reversal is expected to be less than the duration of action of oxycodone in Oxycodone Hydrochloride and Ibuprofen Tablets, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness,

nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression and coma have occurred, but were rare [see **WARNINGS; Cardiovascular Thrombotic Events, Gastrointestinal Bleeding, Ulceration, and Perforation, Hypertension, Renal Toxicity and Hyperkalemia**].

Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdose (5 to 10 times the recommended dosage). Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdose treatment contact a poison control center (1-800-222-1222).

## **DOSAGE AND ADMINISTRATION**

### **Important Dosage and Administration Instructions**

Carefully consider the potential benefits and risks of Oxycodone Hydrochloride and Ibuprofen Tablets and other treatment options before deciding to use. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see **WARNINGS; Cardiovascular Thrombotic Events and WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation**].

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

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with Oxycodone Hydrochloride and Ibuprofen Tablets and adjust the dosage accordingly [see **WARNINGS; Life-Threatening Respiratory Depression**].

### **Initial Dosage**

#### *Initiating Treatment with Oxycodone Hydrochloride and Ibuprofen Tablets*

Initiate treatment with Oxycodone Hydrochloride and Ibuprofen Tablets in a dosing range of one 5 mg/400 mg tablet every 6 hours as needed for pain.

Dosage should not exceed four 5 mg/400 mg tablets in a 24-hour period and should not exceed 7 days.

### **Titration and Maintenance of Therapy**

Individually titrate Oxycodone Hydrochloride and Ibuprofen Tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Oxycodone Hydrochloride and Ibuprofen Tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see **WARNINGS; Addiction, Abuse, and Misuse**]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the Oxycodone Hydrochloride and Ibuprofen Tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

### **Safe Reduction or Discontinuation of Oxycodone Hydrochloride and Ibuprofen Tablets**

Do not abruptly discontinue Oxycodone Hydrochloride and Ibuprofen Tablets in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and

suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

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


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

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

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

## HOW SUPPLIED

Oxycodone Hydrochloride and Ibuprofen Tablets, 5 mg/400 mg are available as follows:

Each yellow, capsule-shaped, film-coated tablet imprinted with  29 on one side and bisect on both sides contains 5 mg of Oxycodone hydrochloride, USP and 400 mg of Ibuprofen, USP. Tablets are supplied in bottles of 30 (NDC 0228-4029-03) and 100 (NDC 0228-4029-11) and 500 (NDC 0228-4029-50).

Dispense in a tight, light-resistant container as defined in the USP.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Store Oxycodone Hydrochloride and Ibuprofen Tablets securely and dispose of properly [see



***PRECAUTIONS; Information for Patients***].

Manufactured by:  
Actavis Elizabeth LLC  
Elizabeth, NJ 07207 USA

Distributed by:  
Actavis Pharma, Inc.  
Parsippany, NJ 07054 USA

Rev. D 4/2019

**Medication Guide**

**Oxycodone Hydrochloride (ox" i koe' done hye" droe klor' ide)  
and Ibuprofen (eye" bue proe' fen) Tablets, CII**

**Oxycodone Hydrochloride and Ibuprofen Tablets are:**

- A strong prescription pain medicine that contains an opioid (narcotic) and a non-steroidal anti-inflammatory drug (NSAID), that is used to manage short-term pain (less than 7 days), 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.
- NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

**Important information about Oxycodone Hydrochloride and Ibuprofen Tablets:**

- **Get emergency help right away if you take too much Oxycodone Hydrochloride and Ibuprofen Tablets (overdose).** When you first start taking Oxycodone Hydrochloride and Ibuprofen 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.
- Taking Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets. They could die from taking it. Selling or giving away Oxycodone Hydrochloride and Ibuprofen Tablets is against the law.
- Store Oxycodone Hydrochloride and Ibuprofen Tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

**Oxycodone Hydrochloride and Ibuprofen Tablets contain an NSAID. NSAIDs can cause serious side effects including:**

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of medicine containing NSAIDs
  - with longer use of medicine containing NSAIDs

**Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG).”**

**Avoid taking NSAIDs, after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart**

**attack.**

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - any time during use
  - without warning symptoms
  - that may cause death

**The risk of getting an ulcer or bleeding increases with:**

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called “corticosteroids”, “anticoagulants”, “SSRIs”, or “SNRIs”
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

**Do not take Oxycodone Hydrochloride and Ibuprofen Tablets:**

- if you have severe asthma, trouble breathing, or other lung problems
- if you have a bowel blockage or have narrowing of the stomach or intestines
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs, or opioid medicine.
- right before or after heart bypass surgery

**Before taking Oxycodone Hydrochloride and Ibuprofen Tablets, tell your healthcare provider if you have a history of:**

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- have high blood pressure
- have asthma
- abuse of street or prescription drugs, alcohol addiction, or mental health problems

**Tell your healthcare provider if you are:**

- **pregnant or planning to become pregnant.** Prolonged use of Oxycodone Hydrochloride and Ibuprofen Tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Talk to your healthcare provider if you are considering taking Oxycodone Hydrochloride and Ibuprofen Tablets during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy.**
- **breastfeeding.** Oxycodone hydrochloride and ibuprofen passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking Oxycodone Hydrochloride and Ibuprofen Tablets with certain other medicines can cause serious side effects that could lead to death.

**When taking Oxycodone Hydrochloride and Ibuprofen Tablets:**

- Do not change your dose. Take Oxycodone Hydrochloride and Ibuprofen Tablets exactly as

prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.

- Take your prescribed dose at the 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 Hydrochloride and Ibuprofen Tablets regularly, do not stop taking Oxycodone Hydrochloride and Ibuprofen Tablets without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen Tablets DO NOT:**

- Drive or operate heavy machinery, until you know how Oxycodone Hydrochloride and Ibuprofen Tablets affect you. Oxycodone Hydrochloride and Ibuprofen 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 Hydrochloride and Ibuprofen tablets may cause you to overdose and die.

**The possible side effects of Oxycodone Hydrochloride and Ibuprofen Tablets:**

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, new or worse high blood pressure, heart failure, liver problems including liver failure, kidney problems including kidney failure, low red blood cells (anemia), life-threatening skin reactions, life-threatening allergic reactions. Call your healthcare provider if you have any of these symptoms and they are severe.

**Get emergency medical help if you have:**

- 
- |  |   |
|--|---|
| • trouble breathing or shortness of breath | • agitation                                 |
| • fast heartbeat                           | • high body temperature                     |
| • chest pain                               | • trouble walking                           |
| • swelling of your face, tongue, or throat | • stiff muscles                             |
| • extreme drowsiness                       | • mental changes such as confusion          |
| • lightheadedness when changing positions  | • weakness in one part or side of your body |
| • fainting or feel faint                   | • slurred speech                            |
- 

**Stop Oxycodone Hydrochloride and Ibuprofen Tablets and call your healthcare provider right away if you have any of the following symptoms:**

- 
- |                                   |  |
|-----------------------------------|--|
| • nausea                          | • flu-like symptoms  |
| • more tired or weaker than usual | • vomit blood  |
| • diarrhea                        | • there is blood in your bowel movement or it is black and |

- diarrhea
  - sticky like tar
  - itching
  - unusual weight gain
  - your skin or eyes look yellow
  - skin rash or blisters with fever
  - indigestion or stomach pain
  - swelling of the arms and legs, hands and feet
- 

**Other information:**

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

These are not all the possible side effects of Oxycodone Hydrochloride and Ibuprofen 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).**

For more information about Oxycodone Hydrochloride and Ibuprofen Tablets, call Actavis at 1-800-432-8534.

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

Manufactured by:  
Actavis Elizabeth LLC  
Elizabeth, NJ 07207 USA

Distributed by:  
Actavis Pharma, Inc.  
Parsippany, NJ 07054 USA

Rev. A 4/2019

**PACKAGE LABEL PRINCIPAL DISPLAY PANEL**

NDC 0228-4029-11

**Oxycodone Hydrochloride and Ibuprofen Tablets**

**5 mg/400 mg**

**PHARMACIST: Dispense the accompanying Medication Guide to each patient.**

**100 Tablets**

**Rx Only**

**Actavis**

NDC 0228-4029-11

# Oxycodone Hydrochloride and Ibuprofen Tablets

**5 mg/400 mg**

PHARMACIST: Dispense the accompanying Medication Guide to each patient.



100 Tablets  
Rx Only



**Each Film-Coated Tablet Contains:**

Oxycodone hydrochloride, USP ..... 5 mg  
Ibuprofen, USP..... 400 mg

Dispense in a tight, light-resistant container as defined in the USP.

**Usual Dosage:** See accompanying package literature for prescribing information.

See Boxed Warning in full prescribing information. **Store** at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep this and all drugs out of the reach of children.

**Manufactured by:**

Actavis Elizabeth LLC  
Elizabeth, NJ 07207 USA

**Distributed by:**

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Parsippany, NJ 07054 USA  
Rev. A 3/2019

LOT/EXP: BELOW



N 3 0228-4029-11 2

52-0237

Non Varnish/Coding Area

## OXYCODONE HYDROCHLORIDE AND IBUPROFEN

oxycodone hydrochloride and ibuprofen tablet, film coated

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0228-4029
Route of Administration	ORAL	DEA Schedule	CII

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OXYCODONE HYDROCHLORIDE (UNII: C1ENJ2TE6C) (OXYCODONE - UNII:CD35PMG570)	OXYCODONE HYDROCHLORIDE	5 mg
IBUPROFEN (UNII: WK2XY110QM) (IBUPROFEN - UNII:WK2XY110QM)	IBUPROFEN	400 mg

### Inactive Ingredients

Ingredient Name	Strength
CALCIUM STEARATE (UNII: 776 XM7047L)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYDROXYPROPYL CELLULOSE (9000 WAMW) (UNII: UKE75GEA7F)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	

### Product Characteristics

<b>Color</b>	YELLOW	<b>Score</b>	2 pieces
<b>Shape</b>	OVAL (capsule-shaped)	<b>Size</b>	17mm
<b>Flavor</b>		<b>Imprint Code</b>	29
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0228-4029-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/04/2008	11/04/2008
2	NDC:0228-4029-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	11/04/2008	
3	NDC:0228-4029-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	11/04/2008	11/04/2008

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078769	11/04/2008	

**Labeler** - Actavis Pharma, Inc. (119723554)

Revised: 4/2019

Actavis Pharma, Inc.