0103584H-02

HYDROCODONE BITARTRATE AND IBUPROFEN TABLETS CII
Rx only
R04/18
0103584H-02

Hydrocodone Bitartrate and Ibuprofen Tablets CII
5 mg/200 mg, 7.5 mg/200 mg and 10 mg/200 mg

Rx only

WARNING: ADDICTION, ABUSE, AND MISUSE; 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
Hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets, and monitor all patients regularly for the development of these behaviors and conditions *(see WARNINGS: Addiction, Abuse, and Misuse)*.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of hydrocodone bitartrate and ibuprofen tablets. Monitor for respiratory depression, especially during initiation of hydrocodone bitartrate and ibuprofen tablets or following a dose increase *(see WARNINGS: Life-Threatening Respiratory Depression)*.

Accidental Ingestion
Accidental ingestion of even one dose of hydrocodone bitartrate and ibuprofen tablets, especially by children, can result in a fatal overdose of hydrocodone *(see WARNINGS: Life-Threatening Respiratory Depression)*.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of hydrocodone bitartrate 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: Neonatal Opioid Withdrawal Syndrome)*.

Cytochrome P450 3A4 Interaction
The concomitant use of hydrocodone bitartrate and ibuprofen tablets with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients taking hydrocodone bitartrate and ibuprofen tablets and any CYP3A4 inhibitor or upon discontinuation of a CYP3A4 inducer for signs and symptoms of respiratory depression and sedation *(see WARNINGS: Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers, PRECAUTIONS: Drug Interactions)*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *(see WARNINGS: Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants, PRECAUTIONS: Drug Interactions)*.
- **Reserve concomitant prescribing of hydrocodone bitartrate 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: Cardiovascular Thrombotic Events)*.**
- **Hydrocodone bitartrate and ibuprofen tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery *(see CONTRAINDICATIONS, WARNINGS: Cardiovascular Thrombotic Events)*.**

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: Gastrointestinal Bleeding, Ulceration, and Perforation)*.

DESCRIPTION

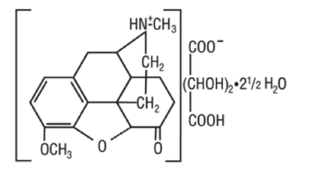
Each hydrocodone bitartrate and ibuprofen tablet 5 mg/200 mg contains:
Hydrocodone Bitartrate, USP .... 5 mg
Ibuprofen, USP .... 200 mg

Each hydrocodone bitartrate and ibuprofen tablet 7.5 mg/200 mg contains:
Hydrocodone Bitartrate, USP...................... 7.5 mg
Ibuprofen, USP .... 200 mg

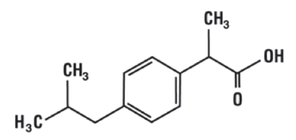
Each hydrocodone bitartrate and ibuprofen tablet 10 mg/200 mg contains:
Hydrocodone Bitartrate, USP .... 10 mg
Ibuprofen, USP .... 200 mg

Hydrocodone bitartrate and ibuprofen tablets are supplied in a fixed combination tablet form for oral administration. Hydrocodone bitartrate and ibuprofen tablets combine the opioid agonist, hydrocodone bitartrate, with the nonsteroidal anti-inflammatory (NSAID) agent, ibuprofen.

Hydrocodone bitartrate is a semisynthetic opioid agonist. Its chemical name is: 4, 5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). Its chemical formula is: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$, and the molecular weight is 494.50. Its structural formula is:



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



Inactive ingredients in hydrocodone bitartrate and ibuprofen tablets include: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium starch glycolate, and titanium dioxide. Also contains hypromellose, polysorbate 80 (5 mg/200 mg and 7.5 mg/200 mg) and talc, glyceryl caprylocaprate, polyvinyl alcohol, D&C red #27, FD&C blue #1 (10 mg/200 mg).

CLINICAL PHARMACOLOGY

Mechanism of Action
Hydrocodone Component
Hydrocodone 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 hydrocodone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with hydrocodone. 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
Hydrocodone 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.

Hydrocodone 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
Hydrocodone 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
Hydrocodone 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: Postmarketing Experience)*. 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 low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *(see ADVERSE REACTIONS: Postmarketing Experience)*.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone 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 hydrocodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *(see DOSAGE AND ADMINISTRATION)*.

Pharmacokinetics
Absorption
After oral dosing with the hydrocodone bitartrate and ibuprofen tablets, a peak hydrocodone plasma level of 27 ng/mL is achieved at 1.7 hours, and a peak ibuprofen plasma level of 30 mcg/mL is achieved at 1.8 hours. The effect of food on the absorption of either component from the hydrocodone bitartrate and ibuprofen tablets has not been established.

Distribution
Ibuprofen is highly protein-bound (99%) like most other non-steroidal anti-inflammatory agents. Although the extent of protein binding of hydrocodone in human plasma has not been definitely determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semisynthetic opioids bind plasma protein to a similar degree (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

Elimination
Metabolism
Hydrocodone exhibits a complex pattern of metabolism, including *O*-demethylation, *N*- demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the *O*-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone. The *O*- and *N*- demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively.

Ibuprofen is present in this product 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'-(2hydroxy-2-methyl-propyl) phenyl propionic acid and (+)-2-4'-(2carboxypropyl) phenyl propionic acid, both of which circulate in the plasma at low levels relative to the parent.

Excretion
Hydrocodone and its metabolites are eliminated primarily in the kidneys, with a mean plasma half-life of 4.5 hours. Ibuprofen is excreted in the urine, 50% to 60% as metabolites and approximately 15% as unchanged drug and conjugate. The plasma half-life is 2.2 hours.

Specific Populations
No significant pharmacokinetic differences based on age or gender have been demonstrated. The pharmacokinetics of hydrocodone and ibuprofen from hydrocodone bitartrate and ibuprofen tablets has not been evaluated in children.

Renal Impairment
The effect of renal insufficiency on the pharmacokinetics of the hydrocodone bitartrate and ibuprofen tablets dosage form has not been determined.

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

In single-dose studies of post surgical pain (abdominal, gynecological, orthopedic), 940 patients were studied at doses of one or two tablets. Hydrocodone bitartrate and ibuprofen tablets produced greater efficacy than placebo and each of its individual components given at the same dose. No advantage was demonstrated for the two-tablet dose.

INDICATIONS AND USAGE

Hydrocodone bitartrate and ibuprofen tablets are indicated for the short-term management of acute 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 hydrocodone bitartrate and ibuprofen tablets and other treatment options before deciding to use hydrocodone bitartrate and ibuprofen tablets. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *(see WARNINGS: Cardiovascular Thrombotic Events, Gastrointestinal Bleeding, Ulceration, and Perforation)*. Do not use hydrocodone bitartrate and ibuprofen tablets for the treatment of conditions such as osteoarthritis or rheumatoid arthritis.

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *(see WARNINGS: Addiction, Abuse, and Misuse)*, reserve hydrocodone bitartrate 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

Hydrocodone bitartrate and ibuprofen tablets are contraindicated in patients with:
- Significant respiratory depression *(see WARNINGS: Life-Threatening Respiratory Depression)*.
- Acute or severe bronchial asthma 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 (e.g., anaphylactic reactions, serious skin reactions) to hydrocodone, ibuprofen, or any components of the drug product *(see WARNINGS: Anaphylactic Reactions, Serious Skin Reactions)*. Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to hydrocodone.
- History of asthma, urticaria, or other 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

Hydrocodone Component
Addiction, Abuse, and Misuse
Hydrocodone bitartrate and ibuprofen tablets contain hydrocodone, a Schedule II controlled substance. As an opioid-containing product, hydrocodone bitartrate and ibuprofen tablets exposes users to the risks of addiction, abuse, and misuse *(see DRUG ABUSE AND DEPENDENCE)*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets, and monitor all patients receiving hydrocodone bitartrate 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 opioid-containing products such as hydrocodone bitartrate and ibuprofen tablets, but use in such patients necessitates intensive counseling about the risks and proper use of hydrocodone bitartrate 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 hydrocodone bitartrate 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.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *(see OVERDOSAGE)*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets.

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

Accidental ingestion of even one dose of hydrocodone bitartrate and ibuprofen tablets, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone bitartrate and ibuprofen tablets.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of hydrocodone bitartrate 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: Pregnancy, Information for Patients)*.

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers
Concomitant use of hydrocodone bitartrate 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 hydrocodone 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 hydrocodone bitartrate and ibuprofen tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in hydrocodone bitartrate and ibuprofen tablets-treated patients may increase hydrocodone plasma concentrations and prolong opioid adverse reactions. When using hydrocodone bitartrate and ibuprofen tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in hydrocodone bitartrate and ibuprofen tablets-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of hydrocodone bitartrate and ibuprofen tablets until stable drug effects are achieved *(see DOSAGE AND ADMINISTRATION, PRECAUTIONS: Drug Interactions)*.

Concomitant use of hydrocodone bitartrate and ibuprofen tablets with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease hydrocodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. When using hydrocodone bitartrate 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 DOSAGE AND ADMINISTRATION, 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 hydrocodone bitartrate 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 hydrocodone bitartrate 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, Information for Patients)*.

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
The use of hydrocodone bitartrate 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: Hydrocodone bitartrate 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 hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets and when hydrocodone bitartrate 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 one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. 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
Hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets. In patients with circulatory shock, hydrocodone bitartrate and ibuprofen tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of hydrocodone bitartrate and ibuprofen tablets in patients with circulatory shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), hydrocodone bitartrate and ibuprofen tablets may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with hydrocodone bitartrate and ibuprofen tablets.

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

Risks of Use in Patients with Gastrointestinal Conditions
Hydrocodone bitartrate and ibuprofen tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The hydrocodone in hydrocodone bitartrate 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 hydrocodone in hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets therapy.

Withdrawal
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 hydrocodone bitartrate and ibuprofen tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *(see PRECAUTIONS: Drug Interactions)*.

When discontinuing hydrocodone bitartrate and ibuprofen tablets in a physically-dependent patient, gradually taper the dosage *(see DOSAGE AND ADMINISTRATION)*. Do not abruptly discontinue hydrocodone bitartrate and ibuprofen tablets in these patients *(see DRUG ABUSE AND DEPENDENCE)*.

Risks of Driving and Operating Machinery
Hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets and know how they will react to the medication *(see PRECAUTIONS: Information for Patients)*.

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, 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 hydrocodone bitartrate and ibuprofen tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If hydrocodone bitartrate and ibuprofen tablets are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Gastrointestinal Bleeding, Ulceration, 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 hydrocodone bitartrate and ibuprofen tablets. 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 NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who used 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 for 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 hydrocodone bitartrate and ibuprofen tablets 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 "flulike" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue hydrocodone bitartrate and ibuprofen tablets immediately, and perform a clinical evaluation of the patient.

Hypertension
NSAID-containing products, including hydrocodone bitartrate 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, thiazide 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 hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If hydrocodone bitartrate 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 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 hydrocodone bitartrate and ibuprofen tablets in patients with advanced renal disease. The renal effects of hydrocodone bitartrate and ibuprofen tablets may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating hydrocodone bitartrate and ibuprofen tablets. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of hydrocodone bitartrate and ibuprofen tablets *(see PRECAUTIONS: Drug Interactions)*. Avoid the use of hydrocodone bitartrate and ibuprofen tablets in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If hydrocodone bitartrate 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, those 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, WARNINGS: 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, hydrocodone bitartrate and ibuprofen tablets are contraindicated in patients with this form of aspirin sensitivity *(see CONTRAINDICATIONS)*. When hydrocodone bitartrate and ibuprofen tablets are used in patients with pre-existing 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 hydrocodone bitartrate and ibuprofen tablets at the first appearance of skin rash or any other sign of hypersensitivity. Hydrocodone bitartrate 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 NSAID-containing products, including hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets have any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAID-containing products, including hydrocodone bitartrate 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 therapy as found in hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets, the possibility of its being related to ibuprofen should be considered.

PRECAUTIONS

Masking of Inflammation and Fever
The pharmacological activity of hydrocodone bitartrate and ibuprofen tablets in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

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) that accompanies each prescription dispensed. Patients, families, or their caregivers should be informed of the following information before initiating therapy with hydrocodone bitartrate and ibuprofen tablets and periodically during the course of ongoing therapy.

1. Addiction, Abuse, and Misuse
   Inform patients that the use of hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets with others and to take steps to protect hydrocodone bitartrate and ibuprofen tablets from theft or misuse.
2. Life-Threatening Respiratory Depression
   Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting hydrocodone bitartrate 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.
3. 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 hydrocodone bitartrate and ibuprofen tablets securely and to dispose of unused hydrocodone bitartrate and ibuprofen tablets appropriately as described below.
4. Interactions with Benzodiazepines and Other CNS Depressants
   Inform patients and caregivers that potentially fatal additive effects may occur if hydrocodone bitartrate and ibuprofen tablets is used with benzodiazepines or 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)*.
5. Serotonin Syndrome
   Inform patients that 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 healthcare providers if they are taking, or plan to take serotonergic medications *(see PRECAUTIONS: Drug Interactions)*.
6. MAOI Interaction
   Inform patients to avoid taking hydrocodone bitartrate and ibuprofen tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking hydrocodone bitartrate and ibuprofen tablets *(see PRECAUTIONS: Drug Interactions)*.
7. Adrenal Insufficiency
   Inform patients that 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: Adrenal Insufficiency)*.
8. Important Administration Instructions
   Instruct patients how to properly take hydrocodone bitartrate and ibuprofen tablets. For the short-term (generally less than 10 days) management of acute pain, the recommended dose of hydrocodone bitartrate and ibuprofen tablets is one tablet every 4 to 6 hours, as necessary. Inform patients that the dosage should not exceed 5 tablets in a 24-hour period *(see DOSAGE AND ADMINISTRATION)*.
9. Hypotension
   Inform patients that hydrocodone bitartrate 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)*.
10. Anaphylaxis
    Inform patients that anaphylaxis has been reported with ingredients contained in hydrocodone bitartrate and ibuprofen tablets. Advise patients how to recognize such a reaction and when to seek medical attention *(see CONTRAINDICATIONS, WARNINGS: Anaphylactic Reactions)*.
11. Pregnancy
    Neonatal Opioid Withdrawal Syndrome
    Inform female patients of reproductive potential that prolonged use of hydrocodone bitartrate and ibuprofen tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *(see Boxed Warning, WARNINGS: Neonatal Opioid Withdrawal Syndrome, PRECAUTIONS: Pregnancy)*.
    Embryo-Fetal Toxicity
    Inform female patients of reproductive potential that hydrocodone bitartrate and ibuprofen tablets can cause fetal harm and to inform the prescriber of a known or suspected pregnancy. Inform pregnant women to avoid use of hydrocodone bitartrate 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 Arteriosis, PRECAUTIONS: Pregnancy)*.
12. 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)*.
13. Infertility
    Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible. Advise female patients of reproductive potential who desire pregnancy that NSAIDs, including hydrocodone bitartrate and ibuprofen tablets, may be associated with a reversible delay in ovulation *(see PRECAUTIONS: Carcinogenicity, Mutagenicity, Impairment of Fertility)*.
14. Driving or Operating Heavy Machinery
    Inform patients that hydrocodone bitartrate and ibuprofen tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *(see WARNINGS: Risks of Driving and Operating Machinery)*.
15. Constipation
    Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *(see ADVERSE REACTIONS: Clinical Trials Experience)*.
16. 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 healthcare provider immediately *(see WARNINGS: Cardiovascular Thrombotic Events)*.
17. Gastrointestinal Bleeding, Ulceration, and Perforation
    Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their healthcare provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding *(see WARNINGS: Gastrointestinal Bleeding, Ulceration, and Perforation)*.
18. 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 hydrocodone bitartrate and ibuprofen tablets and seek immediate medical therapy *(see WARNINGS: Hepatotoxicity)*.
19. 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)*.
20. Serious Skin Reactions
    Advise patients to stop hydrocodone bitartrate 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)*.
21. Avoid Concomitant use of NSAIDs
    Inform patients that the concomitant use of hydrocodone bitartrate 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.
22. Use of NSAIDS and Low-Dose Aspirin
    Inform patients not to use low-dose aspirin concomitantly with hydrocodone bitartrate and ibuprofen tablets until they talk to their healthcare provider *(see PRECAUTIONS: Drug Interactions)*.
23. Ophthalmological Effects
    Instruct patients to report any signs of blurred vision or other eye symptoms *(see PRECAUTIONS: Ophthalmological Effects)*.
24. Disposal of Unused Hydrocodone Bitartrate and Ibuprofen Tablets
    Advise patients to flush the unused tablets down the toilet when hydrocodone bitartrate and ibuprofen tablets are no longer needed or to contact the Drug Enforcement Agency (DEA) to find the location of an authorized collector (1-800-882-9539).

Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients with a CBC and a chemistry profile periodically *(see WARNINGS: Gastrointestinal Bleeding, Ulceration, and Perforation, Renal Toxicity and Hyperkalemia, Hepatotoxicity)*.

Drug Interactions
Inhibitors of CYP3A4 and CYP2D6
The concomitant use of hydrocodone bitartrate and ibuprofen tablets and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir), can increase the plasma concentration of hydrocodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of hydrocodone bitartrate and ibuprofen tablets and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of hydrocodone bitartrate and ibuprofen tablets is achieved *(see WARNINGS: Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers)*.

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone plasma concentration will decrease *(see CLINICAL PHARMACOLOGY: Pharmacokinetics)*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to hydrocodone bitartrate and ibuprofen tablets.

If concomitant use is necessary, consider dosage reduction of hydrocodone bitartrate 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 a dosage increase of hydrocodone bitartrate and ibuprofen tablets until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

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

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

If concomitant use is necessary, consider a dosage increase of hydrocodone bitartrate and ibuprofen tablets until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider hydrocodone bitartrate 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, 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: Life-Threatening Respiratory Depression)*.

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome *(see PRECAUTIONS: Information for Patients)*.

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

Monoamine Oxidase Inhibitors (MAOIs)
MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).

If urgent use of an opioid is necessary with MAOIs such as phenelzine, tranylcypromine, linezolid, 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.

The use of hydrocodone bitartrate and ibuprofen tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics
Agonist/antagonist analgesics such as pentazocine, nalbuphine, butorphanol and buprenorphine may reduce the analgesic effect of hydrocodone bitartrate and ibuprofen tablets and/or precipitate withdrawal symptoms in these patients.

Avoid concomitant use of these drugs.

Muscle Relaxants
Hydrocodone, as well as other opioid analgesics, 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 hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets are used concomitantly with anticholinergic drugs.

Drugs That Interfere With Hemostasis
Ibuprofen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of ibuprofen and anticoagulants has 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 hydrocodone bitartrate and ibuprofen tablets with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding *(see WARNINGS: Hematologic Toxicity)*.

Aspirin
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)*.

Medication Guide
Hydrocodone Bitartrate and Ibuprofen Tablets CII
(hye" droe koe' done bye tar' trate and eye" bue proe' fen)

Hydrocodone bitartrate and ibuprofen tablets is:
- 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 (acute) pain, 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 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, redness, swelling, and inflammation.

Important information about hydrocodone bitartrate and ibuprofen tablets:
- **Get emergency help right away if you take too much hydrocodone bitartrate and ibuprofen tablets (overdose)**. When you first start taking hydrocodone bitartrate 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 hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets. They could die from taking it. Store hydrocodone bitartrate and ibuprofen tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away hydrocodone bitartrate and ibuprofen tablets is against the law.

Hydrocodone bitartrate 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
- increasing doses of NSAIDS
- longer use of NSAIDS
- smoking
- drinking alcohol
- taking medicines called "corticosteroids," "anticoagulants," "SSRIs," or "SNRIs"
- older age
- poor health
- advanced liver disease
- bleeding problems

Do not take hydrocodone bitartrate 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, other NSAIDs, or opioid medicine.
- right before or after heart bypass surgery.

Before taking hydrocodone bitartrate and ibuprofen tablets, tell your healthcare provider if you have a history of:
- head injury or seizures
- problems urinating
- high blood pressure
- liver, kidney, or thyroid problems
- pancreas or gallbladder problems
- 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.** Talk to your healthcare provider if you are considering taking hydrocodone bitartrate and ibuprofen tablets during pregnancy. Prolonged use of hydrocodone bitartrate and ibuprofen tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. **You should not take NSAIDs after 29 weeks of pregnancy.**
- **breastfeeding or planning to breastfeed.** Hydrocodone bitartrate and ibuprofen tablets pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking hydrocodone bitartrate and ibuprofen tablets with certain other medicines can cause serious side effects that could lead to death.

When taking hydrocodone bitartrate and ibuprofen tablets:
- Do not change your dose. Take hydrocodone bitartrate and ibuprofen tablets exactly as prescribed by your healthcare provider.
  Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 4 to 6 hours, as needed. 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 hydrocodone bitartrate and ibuprofen tablets regularly, do not stop taking it without talking to your healthcare provider.
- After you stop taking hydrocodone bitartrate and ibuprofen tablets, flush any unused tablets down the toilet or contact the Drug Enforcement Agency (DEA) to find the location of an authorized collector (1-800-882-9539) after you stop taking hydrocodone bitartrate and ibuprofen tablets.

While taking hydrocodone bitartrate and ibuprofen tablets DO NOT:
- drive or operate heavy machinery, until you know how it affects you. Hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets may cause you to overdose and die.

Medication Guide
Hydrocodone Bitartrate and Ibuprofen Tablets CII
(hye" droe koe' done bye tar' trate and eye" bue proe' fen)

Hydrocodone bitartrate and ibuprofen tablets is:
- 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 (acute) pain, 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 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, redness, swelling, and inflammation.

Important information about hydrocodone bitartrate and ibuprofen tablets:
- **Get emergency help right away if you take too much hydrocodone bitartrate and ibuprofen tablets (overdose)**. When you first start taking hydrocodone bitartrate 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 hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets. They could die from taking it. Store hydrocodone bitartrate and ibuprofen tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away hydrocodone bitartrate and ibuprofen tablets is against the law.

Hydrocodone bitartrate 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
- increasing doses of NSAIDS
- longer use of NSAIDS
- smoking
- drinking alcohol
- taking medicines called "corticosteroids," "anticoagulants," "SSRIs," or "SNRIs"
- older age
- poor health
- advanced liver disease
- bleeding problems

Do not take hydrocodone bitartrate 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, other NSAIDs, or opioid medicine.
- right before or after heart bypass surgery.

Before taking hydrocodone bitartrate and ibuprofen tablets, tell your healthcare provider if you have a history of:
- head injury or seizures
- problems urinating
- high blood pressure
- liver, kidney, or thyroid problems
- pancreas or gallbladder problems
- 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.** Talk to your healthcare provider if you are considering taking hydrocodone bitartrate and ibuprofen tablets during pregnancy. Prolonged use of hydrocodone bitartrate and ibuprofen tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. **You should not take NSAIDs after 29 weeks of pregnancy.**
- **breastfeeding or planning to breastfeed.** Hydrocodone bitartrate and ibuprofen tablets pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking hydrocodone bitartrate and ibuprofen tablets with certain other medicines can cause serious side effects that could lead to death.

When taking hydrocodone bitartrate and ibuprofen tablets:
- Do not change your dose. Take hydrocodone bitartrate and ibuprofen tablets exactly as prescribed by your healthcare provider.
  Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 4 to 6 hours, as needed. 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 hydrocodone bitartrate and ibuprofen tablets regularly, do not stop taking it without talking to your healthcare provider.
- After you stop taking hydrocodone bitartrate and ibuprofen tablets, flush any unused tablets down the toilet or contact the Drug Enforcement Agency (DEA) to find the location of an authorized collector (1-800-882-9539) after you stop taking hydrocodone bitartrate and ibuprofen tablets.

While taking hydrocodone bitartrate and ibuprofen tablets DO NOT:
- drive or operate heavy machinery, until you know how it affects you. Hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets may cause you to overdose and die.

Concomitant use of hydrocodone bitartrate and ibuprofen tablets and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding *(see WARNINGS: 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 hydrocodone bitartrate 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, coadministration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. Monitor for signs of worsening renal function *(see WARNINGS: Renal Toxicity and Hyperkalemia)*. These effects are usually reversible.

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

During concomitant use of hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets and methotrexate, monitor patients for methotrexate toxicity.

Cyclosporine
Concomitant use of hydrocodone bitartrate and ibuprofen tablets and cyclosporine may increase cyclosporine's nephrotoxicity.

During concomitant use of hydrocodone bitartrate 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 hydrocodone bitartrate 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 hydrocodone bitartrate 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.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Carcinogenesis
Long-term animal studies to evaluate the carcinogenic potential of the combination of hydrocodone and ibuprofen, ibuprofen alone, or hydrocodone alone have not been conducted.

Mutagenesis
The mutagenic potential of the combination of hydrocodone and ibuprofen or hydrocodone alone has not been investigated.

In published studies, ibuprofen was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames assay).

Impairment of Fertility
Animal studies evaluating the impact of the combination of hydrocodone and ibuprofen or hydrocodone alone on fertility have not been conducted.

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 (0.2-times the MRHD of 1000 mg ibuprofen 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 (0.03-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.

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including ibuprofen, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAID-containing products, including hydrocodone bitartrate and ibuprofen tablets, in women who have difficulties conceiving or who are undergoing investigation of infertility.

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

Pregnancy

Risk Summary
Use of drug products containing NSAIDs, including hydrocodone bitartrate and ibuprofen tablets, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including hydrocodone bitartrate and ibuprofen tablets, in pregnant women starting at 30 weeks gestation (third trimester). Prolonged use of opioid analgesics during pregnancy can cause neonatal opioid withdrawal syndrome *(see WARNINGS: Neonatal Opioid Withdrawal Syndrome)*. There are no available data with hydrocodone bitartrate and ibuprofen tablets in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

In animal reproduction studies, an increase in the percentage of litters and fetuses with any major abnormality and an increase in the number of litters and fetuses with one or more nonossified metacarpals was observed when the combination of hydrocodone and ibuprofen was administered orally to pregnant rabbits during organogenesis at 1.8 times the maximum daily dose. There are no animal reproductive and developmental toxicology studies with hydrocodone alone.

In published animal reproduction studies testing ibuprofen alone, there were no clear developmental effects at doses up to 1.2 times the maximum recommended human dose (MRHD) in the rabbit and 1.8 times in the MRHD rat when dosed throughout gestation. In contrast, an increase in membranous ventricular septal defects was reported in rats treated on Gestation Days 9 & 10 with 3 times the MRHD. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as ibuprofen, resulted in increased pre- and post-implantation loss (*see Data*). Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Fetal/neonatal adverse reactions
Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *(see WARNINGS: Neonatal Opioid Withdrawal Syndrome)*.

Labor and Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

There are no studies on the effects of hydrocodone bitartrate and ibuprofen tablets during labor or delivery. In animal studies, NSAIDs, including ibuprofen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Hydrocodone bitartrate and ibuprofen tablets are not recommended for use in women during and immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including hydrocodone bitartrate and ibuprofen tablets, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data
Animal Data
Pregnant rabbits were treated with 10, 33, or 95 mg/kg of 1:27 ratio of hydrocodone:ibuprofen (the high dose is 1.8 times the maximum daily dose of both compounds based on surface area) from Gestation Day 5 to 18. The dose of 95 mg/kg of the combination, which also produced maternal toxicity (44% decrease in body weight gain compared to control), resulted in an increase in the percentage of litters and fetuses with any major abnormality and an increase in the number of litters and fetuses with one or more nonossified metacarpals (a minor abnormality).

Pregnant rats were treated with 50, 100, or 166 mg/kg of a 1:27 ratio of hydrocodone:ibuprofen (the high dose is 1.6 times the maximum daily dose of both compounds based on body surface area) from Gestation Day 5 to 15. No reproductive toxicity was noted despite the presence of maternal toxicity in the 100 and 166 mg/kg groups (21% and 60% decrease in body weight gain compared to control).

In a published study, female rabbits given 7.5, 20, or 60 mg/kg ibuprofen (0.15, 0.39, or 1.2 times the maximum recommended human daily dose of 1000 mg of ibuprofen based on body surface area) from Gestation Days 1 to 29, no clear treatment-related adverse developmental effects were noted. This dose was associated with significant maternal toxicity (stomach ulcers, gastric lesions). In the same publication, female rats were administered 7.5, 20, 60, 180 mg/kg ibuprofen (0.07, 0.2, 0.6, 1.8 times the maximum daily dose) did not result in clear adverse developmental effects. Maternal toxicity (gastrointestinal lesions) was noted at 20 mg/kg and above.

In a published study, rats were orally dosed with 300 mg/kg ibuprofen (3 times the maximum human daily dose of 1000 mg based on body surface area) during Gestation Days 9 and 10 (critical time points for heart development in rats). Ibuprofen treatment resulted in an increase in the incidence of membranous ventricular septal defects. This dose was associated with significant maternal toxicity including gastrointestinal toxicity (1 out of 20 animals). In the same study/publication rabbits were dosed on Gestation Day 9, 10 and 11 with 500 mg/kg (9.7 times the maximum human daily dose), and only one incidence each of a membranous ventricular septal defect and gastroschisis was noted in the rabbit fetuses. This dose was also associated with maternal toxicity.

Nursing Mothers

Risk Summary
Hydrocodone is present in human milk. A published lactation study reports variable concentrations of hydrocodone and hydromorphone (an active metabolite) in breast milk with administration of immediate-release hydrocodone to nursing mothers in the early post-partum period. This lactation study did not assess breastfed infants for potential adverse drug reactions.

Limited published literature reports that, following oral administration, ibuprofen is present in human milk at relative infant doses of 0.06% to 0.6% of the maternal weight-adjusted daily dose. Lactation studies have not been conducted with hydrocodone bitartrate and ibuprofen tablets, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

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

Clinical Considerations
Monitor infants exposed to hydrocodone bitartrate and ibuprofen tablets through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of hydrocodone is stopped, or when breastfeeding is stopped.

Pediatric Use
The safety and effectiveness of hydrocodone bitartrate and ibuprofen tablets in pediatric patients below the age of 16 have not been established.

Geriatric Use
In controlled clinical trials there was no difference in tolerability between patients < 65 years of age and those ≥ 65, apart from an increased tendency of the elderly to develop constipation. However, elderly patients are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and renal adverse reactions as well as possible increased risk of respiratory depression with opioids. 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 *(see WARNINGS: Cardiovascular Thrombotic Events, Gastrointestinal Bleeding, Ulceration, and Perforation, Renal Toxicity and Hyperkalemia)*.

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 hydrocodone bitartrate and ibuprofen tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *(see WARNINGS: Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients)*.

Both hydrocodone 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
Patients with hepatic impairment may have higher hydrocodone plasma concentrations than those with normal function. In patients with severe hepatic impairment, use a low initial dose. Monitor these patients closely for adverse events such as respiratory depression, sedation, and hypotension.

Renal Impairment
Patients with renal impairment may have higher hydrocodone plasma concentrations than those with normal function. Use a low initial dose in patients with renal impairment and monitor closely for adverse events such as respiratory depression, sedation, and hypotension.

ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the labeling including the WARNINGS section.

- Addiction, Abuse, and Misuse
- Life-Threatening Respiratory Depression
- Neonatal Opioid Withdrawal Syndrome
- Interactions with Cytochrome P450 3A4 Inhibitors and Inducers
- Interactions with Benzodiazepines or Other CNS Depressants
- Adrenal Insufficiency
- Severe Hypotension
- Seizures
- Withdrawal
- Cardiovascular Thrombotic Events
- Gastrointestinal Bleeding, Ulceration, and Perforation
- Hepatotoxicity
- Hypertension
- Heart Failure and Edema
- Renal Toxicity and Hyperkalemia
- Anaphylactic Reactions
- Exacerbation of Asthma Related to Aspirin Sensitivity
- Serious Skin Reactions
- Premature Closure of Fetal Ductus Arteriosus
- Hematologic Toxicity
- Aseptic Meningitis

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.

Hydrocodone bitartrate and ibuprofen tablets was administered to approximately 300 pain patients in a safety study that employed dosages and a duration of treatment sufficient to encompass the recommended usage *(see DOSAGE AND ADMINISTRATION)*. Adverse event rates generally increased with increasing daily dose. The event rates reported below are from approximately 150 patients who were in a group that received one tablet of hydrocodone bitartrate and ibuprofen tablets an average of three to four times daily. The overall incidence rates of adverse experiences in the trials were fairly similar for this patient group and those who received the comparison treatment, acetaminophen 600 mg with codeine 60 mg. The following lists adverse events that occurred with an incidence of 1% or greater in clinical trials of hydrocodone bitartrate and ibuprofen tablets, without regard to the causal relationship of the events to the drug. To distinguish different rates of occurrence in clinical studies, the adverse events are listed as follows:

name of adverse event = less than 3%
*adverse events marked with an asterisk * = 3% to 9%*
adverse event rates over 9% are in parentheses.

Body as a Whole
Abdominal pain*; Asthenia*; Fever; Flu syndrome; Headache (27%); Infection*; Pain.

Cardiovascular
Palpitations; Vasodilation.

Central Nervous System
Anxiety*; Confusion; Dizziness (14%); Hypertonia; Insomnia*; Nervousness*; Paresthesia; Somnolence (22%); Thinking abnormalities.

Digestive
Anorexia; Constipation (22%); Diarrhea*; Dry mouth*; Dyspepsia (12%); Flatulence*; Gastritis; Melena; Mouth ulcers; Nausea (21%); Thirst; Vomiting*.

Metabolic and Nutritional Disorders
Edema*.

Respiratory
Dyspnea; Hiccups; Pharyngitis; Rhinitis.

Skin and Appendages
Pruritus*; Sweating*.

Special Senses
Tinnitus.

Urogenital
Urinary frequency.

Incidence less than 1%

Body as a Whole
Allergic reaction.

Cardiovascular
Arrhythmia; Hypotension; Tachycardia.

Central Nervous System
Agitation; Abnormal dreams; Decreased libido; Depression; Euphoria; Mood changes; Neuralgia; Slurred speech; Tremor, Vertigo.

Digestive
Chalky stool; "Clenching teeth"; Dysphagia; Esophageal spasm; Esophagitis; Gastroenteritis; Glossitis; Liver enzyme elevation.

Metabolic and Nutritional
Weight decrease.

Musculoskeletal
Arthralgia; Myalgia.

Respiratory
Asthma; Bronchitis; Hoarseness; Increased cough; Pulmonary congestion; Pneumonia; Shallow breathing; Sinusitis.

Skin and Appendages
Rash; Urticaria.

Special Senses
Altered vision; Bad taste; Dry eyes.

Urogenital
Cystitis; Glycosuria; Impotence; Urinary incontinence; Urinary retention.

Postmarketing Experience
The following adverse reactions have been identified during post approval use of hydrocodone. 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 hydrocodone bitartrate and ibuprofen tablets.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *(see CLINICAL PHARMACOLOGY: Pharmacodynamics)*.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
Hydrocodone bitartrate and ibuprofen tablets contain hydrocodone, a Schedule II controlled substance.

Abuse
Hydrocodone bitartrate and ibuprofen tablets contains hydrocodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Hydrocodone bitartrate and ibuprofen tablets can be abused and is 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 with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among 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. Healthcare 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.

Hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets
Abuse of hydrocodone bitartrate and ibuprofen tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of hydrocodone bitartrate and ibuprofen tablets with alcohol and other central nervous system depressants *(see WARNINGS: Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants)*.

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

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

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (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.

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

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

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone and/or ibuprofen.

Clinical Presentation

Hydrocodone Component
Acute overdose with opioids 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 re-establishment 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 hydrocodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydrocodone overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of hydrocodone, 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.

Manage patients with symptomatic and supportive care following an NSAID overdosage. 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, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of hydrocodone bitartrate and ibuprofen tablets and other treatment options before deciding to use hydrocodone bitartrate and ibuprofen tablets. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *(see WARNINGS: Cardiovascular Thrombotic Events, 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 hydrocodone bitartrate and ibuprofen tablets and adjust the dosage accordingly *(see WARNINGS: Life-Threatening Respiratory Depression)*.

After observing the response to initial therapy with hydrocodone bitartrate and ibuprofen tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

Initial Dosage
For the short-term (generally less than 10 days) management of acute pain, the recommended dose of hydrocodone bitartrate and ibuprofen tablets is one tablet every 4 to 6 hours, as necessary. Dosage should not exceed 5 tablets in a 24-hour period. It should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The lowest effective dose or the longest dosing interval should be sought for each patient *(see WARNINGS)*, especially in the elderly. After observing the initial response to therapy with hydrocodone bitartrate and ibuprofen tablets, the dose and frequency of dosing should be adjusted to suit the individual patient's need, without exceeding the total daily dose recommended.

Titration and Maintenance of Therapy
Individually titrate hydrocodone bitartrate and ibuprofen tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving hydrocodone bitartrate 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 hydrocodone bitartrate 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.

Discontinuation of hydrocodone bitartrate and ibuprofen tablets
When a patient who has been taking hydrocodone bitartrate and ibuprofen tablets regularly and may be physically dependent no longer requires therapy with hydrocodone bitartrate and ibuprofen tablets, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue hydrocodone bitartrate and ibuprofen tablets in a physically dependent patient *(see WARNINGS: Addiction, Abuse, and Misuse, DRUG ABUSE AND DEPENDENCE)*.

HOW SUPPLIED

Hydrocodone Bitartrate and Ibuprofen Tablets 5 mg/200 mg are white, film-coated, oval shaped, scored tablets, debossed "3584" on one side and debossed "V" on the reverse side.

They are supplied as follows:
- Bottles of 100: NDC 0603-3584-21

Hydrocodone Bitartrate and Ibuprofen Tablets 7.5 mg/200 mg are white, film-coated, round, debossed "3585" on one side and debossed "V" on the reverse side.

They are supplied as follows:
- Bottles of 100: NDC 0603-3897-21
- Bottles of 500: NDC 0603-3897-28

Hydrocodone Bitartrate and Ibuprofen Tablets 10 mg/200 mg are purple, film-coated, oval shaped, scored tablets, debossed "3586" on one side and debossed "V" on the reverse side.

They are supplied as follows:
- Bottles of 100: NDC 0603-3586-21

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

Dispense in a tight, light-resistant container.

A Schedule CS-II Controlled Substance.

Medication Guide
Hydrocodone Bitartrate and Ibuprofen Tablets
(hye" droe koe' done bye tar' trate and eye" bue proe' fen) CII

Hydrocodone bitartrate and ibuprofen tablets is:
- 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 (acute) pain, 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 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, redness, swelling, and inflammation.

Important information about hydrocodone bitartrate and ibuprofen tablets:
- **Get emergency help right away if you take too much hydrocodone bitartrate and ibuprofen tablets (overdose)**. When you first start taking hydrocodone bitartrate 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 hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets. They could die from taking it. Store hydrocodone bitartrate and ibuprofen tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away hydrocodone bitartrate and ibuprofen tablets is against the law.

Hydrocodone bitartrate 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
- increasing doses of NSAIDS
- longer use of NSAIDS
- smoking
- drinking alcohol
- taking medicines called "corticosteroids," "anticoagulants," "SSRIs," or "SNRIs"
- older age
- poor health
- advanced liver disease
- bleeding problems

Do not take hydrocodone bitartrate 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, other NSAIDs, or opioid medicine.
- right before or after heart bypass surgery.

Before taking hydrocodone bitartrate and ibuprofen tablets, tell your healthcare provider if you have a history of:
- head injury or seizures
- problems urinating
- high blood pressure
- liver, kidney, or thyroid problems
- pancreas or gallbladder problems
- 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.** Talk to your healthcare provider if you are considering taking hydrocodone bitartrate and ibuprofen tablets during pregnancy. Prolonged use of hydrocodone bitartrate and ibuprofen tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. **You should not take NSAIDs after 29 weeks of pregnancy.**
- **breastfeeding or planning to breastfeed.** Hydrocodone bitartrate and ibuprofen tablets pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking hydrocodone bitartrate and ibuprofen tablets with certain other medicines can cause serious side effects that could lead to death.

When taking hydrocodone bitartrate and ibuprofen tablets:
- Do not change your dose. Take hydrocodone bitartrate and ibuprofen tablets exactly as prescribed by your healthcare provider.
  Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 4 to 6 hours, as needed. 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 hydrocodone bitartrate and ibuprofen tablets regularly, do not stop taking it without talking to your healthcare provider.
- After you stop taking hydrocodone bitartrate and ibuprofen tablets, flush any unused tablets down the toilet or contact the Drug Enforcement Agency (DEA) to find the location of an authorized collector (1-800-882-9539) after you stop taking hydrocodone bitartrate and ibuprofen tablets.

While taking hydrocodone bitartrate and ibuprofen tablets DO NOT:
- drive or operate heavy machinery, until you know how it affects you. Hydrocodone bitartrate 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 hydrocodone bitartrate and ibuprofen tablets may cause you to overdose and die.

The possible side effects of hydrocodone bitartrate and ibuprofen tablets:
- constipation, diarrhea, gas, heartburn, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, heart attack, stroke, new or worse high blood pressure, heart failure, liver problems including liver failure, kidney problems including kidney failure, bleeding and ulcers in the stomach and intestine, low red blood cells (anemia), life-threatening skin reactions, life-threatening allergic reactions, asthma attacks in people who have asthma. 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
- fast heartbeat
- chest pain
- swelling of your face, tongue, or throat
- extreme drowsiness
- lightheadedness when changing positions
- a fainting spell
- agitation
- high body temperature
- trouble walking
- stiff muscles
- mental changes such as confusion
- weakness in one part or side of your body
- slurred speech

Stop hydrocodone bitartrate and ibuprofen tablets and call your healthcare provider right away if you have any of the following symptoms:
- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the possible side effects of hydrocodone bitartrate 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, www.parpharm.com or call 1-800-828-9393.**

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.
- Do not take other NSAID medicines, even those sold in lower doses without a prescription (over-the-counter) while taking hydrocodone bitartrate and ibuprofen tablets. NSAIDs may be present in over-the-counter medications for treatment of colds, fever, or insomnia.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

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

Revised: 04/18 OS3584H-01-1-02

The possible side effects of hydrocodone bitartrate and ibuprofen tablets:
- constipation, diarrhea, gas, heartburn, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, heart attack, stroke, new or worse high blood pressure, heart failure, liver problems including liver failure, kidney problems including kidney failure, bleeding and ulcers in the stomach and intestine, low red blood cells (anemia), life-threatening skin reactions, life-threatening allergic reactions, asthma attacks in people who have asthma. 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
- fast heartbeat
- chest pain
- swelling of your face, tongue, or throat
- extreme drowsiness
- lightheadedness when changing positions
- a fainting spell
- agitation
- high body temperature
- trouble walking
- stiff muscles
- mental changes such as confusion
- weakness in one part or side of your body
- slurred speech

Stop hydrocodone bitartrate and ibuprofen tablets and call your healthcare provider right away if you have any of the following symptoms:
- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the possible side effects of hydrocodone bitartrate 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, www.parpharm.com or call 1-800-828-9393.**

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.
- Do not take other NSAID medicines, even those sold in lower doses without a prescription (over-the-counter) while taking hydrocodone bitartrate and ibuprofen tablets. NSAIDs may be present in over-the-counter medications for treatment of colds, fever, or insomnia.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

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

Revised: 04/18 OS3584H-01-1-02

The possible side effects of hydrocodone bitartrate and ibuprofen tablets:
- constipation, diarrhea, gas, heartburn, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, heart attack, stroke, new or worse high blood pressure, heart failure, liver problems including liver failure, kidney problems including kidney failure, bleeding and ulcers in the stomach and intestine, low red blood cells (anemia), life-threatening skin reactions, life-threatening allergic reactions, asthma attacks in people who have asthma. 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
- fast heartbeat
- chest pain
- swelling of your face, tongue, or throat
- extreme drowsiness
- lightheadedness when changing positions
- a fainting spell
- agitation
- high body temperature
- trouble walking
- stiff muscles
- mental changes such as confusion
- weakness in one part or side of your body
- slurred speech

Stop hydrocodone bitartrate and ibuprofen tablets and call your healthcare provider right away if you have any of the following symptoms:
- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the possible side effects of hydrocodone bitartrate 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, www.parpharm.com or call 1-800-828-9393.**

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.
- Do not take other NSAID medicines, even those sold in lower doses without a prescription (over-the-counter) while taking hydrocodone bitartrate and ibuprofen tablets. NSAIDs may be present in over-the-counter medications for treatment of colds, fever, or insomnia.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

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

Revised: 04/18 OS3584H-01-1-02