

**HYDROCODONE BITARTRATE AND ASPIRIN- hydrocodone bitartrate and
aspirin tablet
LGM PHARMA SOLUTIONS, LLC**

Hydrocodone Bitartrate with Aspirin

HYDROCODONE BITARTRATE and ASPIRIN TABLETS CII

Revised: January 2024

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF HYDROCODONE BITARTRATE AND ASPIRIN TABLETS

Addition, Abuse and Misuse

Because the use of Hydrocodone Bitartrate and Aspirin Tablets exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions [see Warnings].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Hydrocodone Bitartrate and Aspirin Tablets, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of Hydrocodone Bitartrate and Aspirin Tablets are essential [see Warnings].

Accidental Ingestion

Accidental ingestion of even one dose of Hydrocodone Bitartrate and Aspirin Tablets, especially by children, can result in a fatal overdose of hydrocodone [see Warnings].

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. Reserve concomitant prescribing of Hydrocodone Bitartrate and Aspirin Tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate [see Warnings, Precautions; Drug Interactions].

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery [see Warnings].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

Healthcare providers are strongly encouraged to complete a REMS complaint education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription [see Warnings].

Cytochrome P450 3A4 Interaction

The concomitant use of Hydrocodone Bitartrate and Aspirin Tablets with all Cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory

depression. In addition, discontinuation of a concomitantly used Cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentrations. Monitor patients receiving Hydrocodone Bitartrate and Aspirin Tablets and any Cytochrome P450 3A4 inhibitor or inducer for signs of respiratory depression or sedation [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

DESCRIPTION

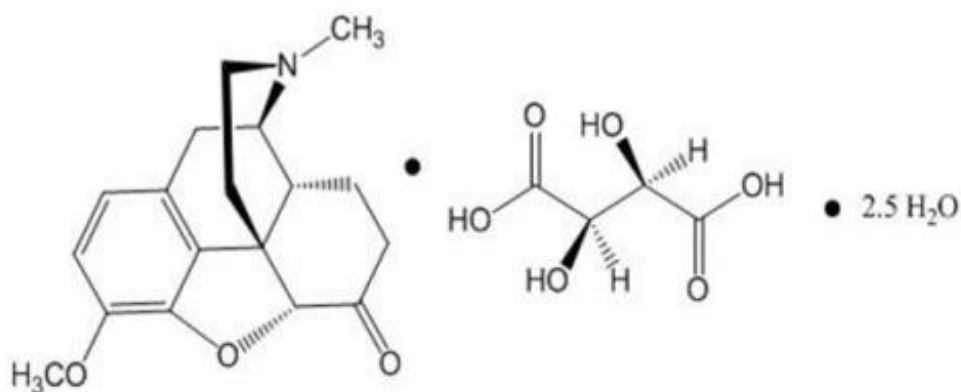
Hydrocodone Bitartrate and Aspirin Tablets are immediate-release tablets for oral administration only.

Each Hydrocodone Bitartrate and Aspirin Tablet, 5 mg/500 mg contains:

Hydrocodone Bitartrate 5 mg

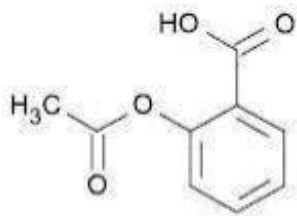
Aspirin 500 mg

Hydrocodone Bitartrate is an opioid agonist and occurs as fine, white crystals or as a crystalline powder. It is affected by light. It is soluble in water, slightly soluble in alcohol, and insoluble in ether and chloroform. The chemical name is: 4,5 α -epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



Hydrocodone Bitartrate
 $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2.5 H_2O$
Molecular weight = 494.5

Aspirin, acetylsalicylic acid, is a nonsteroidal anti-inflammatory drug which is an odorless white, needle-like crystalline or powdery substance. The aspirin component is 2-(acetyloxy)-, Benzoic acid. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary-odor. It is highly lipid soluble and slightly soluble in water; freely soluble in alcohol; soluble in chloroform and in ether; sparingly soluble in absolute ether. Its structure is as follows:



Aspirin

$C_9H_8O_4$

Molecular Weight 108.16

In addition, each tablet contains the following inactive ingredients: Microcrystalline Cellulose, Anhydrous Lactose, Corn Starch, Hypromellose, Crospovidone, Stearic Acid, Talc, Colloidal Silicon Dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Hydrocodone is full opioid agonist with relative selectivity for the mu-opioid (μ) 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.

Aspirin is a nonsteroidal anti-inflammatory drug. Aspirin (acetylsalicylic acid) is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclo-oxygenase via acetylation.

Aspirin (acetylsalicylic acid) works by inhibiting the body's production of prostaglandins, including prostaglandins involved in inflammation. Prostaglandins cause pain sensations by stimulating muscle contractions and dilating blood vessels throughout the body. In the CNS, aspirin works on the hypothalamus heat-regulating center to reduce fever, however, other mechanisms may be involved.

Pharmacodynamics

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A₂. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I₂ (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

At higher doses aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-oxygenase inhibition in peripheral tissues. In vitro studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated. It is this nonspecific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation. [see **ADVERSE REACTIONS**].

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.

Aspirin can produce gastrointestinal injury (lesions, ulcers) through a mechanism that is not yet completely understood, but may involve a reduction in eicosanoid synthesis by the gastric mucosa. Decreased production of prostaglandins may compromise the defenses of the gastric mucosa and the activity of substances involved in tissue repair and ulcer healing.

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**]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The casual role of opioids in the syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone

levels have not been adequately controlled for in studies conducted to date [see **ADVERSE REACTIONS**].

Effects on the Immune System

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

Concentration-Efficacy Relationships

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

The dose of Hydrocodone Bitartrate and Aspirin Tablets must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients [see **DOSAGE AND ADMINISTRATION**].

Pharmacokinetics

The behavior of the individual components is described below.

Hydrocodone

Absorption:

Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours.

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 -hydroxymetabolites. CYP3A4 mediated N-demethylation to norhydrocodone is the primary metabolic pathway of hydrocodone with a lower contribution from CYP2D6 mediated O-demethylation to hydromorphone. Hydromorphone is formed from the O-demethylation of hydrocodone and may contribute to the total analgesic effect of hydrocodone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs [see **PRECAUTIONS; Drug Interactions**]. N-demethylation of hydrocodone to form norhydrocodone via CYP3A4 while O-demethylation of hydrocodone to hydromorphone is predominantly catalyzed by CYP2D6 and to a lesser extent by an unknown low affinity CYP enzyme.

Excretion

Hydrocodone and its metabolites are eliminated primarily in the kidneys.

Aspirin

Absorption:

In general, immediate release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing [see **Pharmacokinetics—Metabolism**]. The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents), and other physiologic factors.

Distribution:

Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent, *i.e.*, nonlinear. At low concentrations (<100 micrograms/milliliter ([micro]g/mL)), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (>400 [micro]g/mL), only about 75 percent is bound.

Elimination:

Metabolism

Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 grams (g)), the plasma half-life may be increased to over 20 hours.

Excretion

The elimination of salicylic acid follows zero order pharmacokinetics; (*i.e.*, the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5 percent to >80 percent. Following therapeutic doses, approximately 10 percent is found excreted in the urine as salicylic acid, 75 percent as salicyluric acid, and 10 percent phenolic and 5 percent acyl glucuronides of salicylic acid.

INDICATIONS AND USAGE

Hydrocodone Bitartrate and Aspirin Tablets are indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, which can occur at any dosage or duration, reserve Hydrocodone Bitartrate and Aspirin 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.

Hydrocodone Bitartrate and Aspirin Tablets should not be used for extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

CONTRADICTIONS

Hydrocodone Bitartrate and Aspirin Tablets are contraindicated in patients with:

- Significant respiratory depression [see **WARNINGS**]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see **WARNINGS**]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see **WARNINGS**]
- Hypersensitivity to hydrocodone or aspirin (e.g., angioedema) [see **WARNINGS**]
- Hemophilia [see **WARNINGS**]
- Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses [see **WARNINGS**]
- Known allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) [see **WARNINGS, PRECAUTIONS**]
- Syndrome of asthma, rhinitis, and nasal polyps [see **WARNINGS, PRECAUTIONS**]

WARNINGS

Addiction, Abuse, Misuse

Hydrocodone Bitartrate and Aspirin Tablets contain hydrocodone, a Schedule II controlled substance. As an opioid, Hydrocodone Bitartrate and Aspirin Tablets expose users to the risks of addiction, abuse, and misuse [see **DRUG ABUSE AND DEPENDENCE**].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Hydrocodone Bitartrate and Aspirin 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 Aspirin Tablets, and reassess all patients receiving Hydrocodone Bitartrate and Aspirin Tablets for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Hydrocodone Bitartrate and Aspirin Tablets, but use in such patients

necessitates intensive counseling about the risks and proper use of Hydrocodone Bitartrate and Aspirin Tablets along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [see **WARNINGS; Life-Threatening Respiratory Depression, DOSAGE AND ADMINISTRATION; Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose**].

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing Hydrocodone Bitartrate and Aspirin Tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and proper disposal of unused drug. 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 (CO₂) 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 Aspirin Tablets, the risk is greatest during the initiation of therapy or following a dosage increase.

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

Accidental ingestion of Hydrocodone Bitartrate and Aspirin Tablets, especially by children, can result in respiratory depression and death due to an overdose of Hydrocodone Bitartrate and Aspirin Tablets.

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

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper [see **DOSAGE AND ADMINISTRATION**].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for personal access to naloxone, both when initiating and renewing treatment with Hydrocodone Bitartrate and

Aspirin Tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered [see **PRECAUTIONS; Information for Patients/Caregivers**].

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone when there are household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone [see **DOSAGE AND ADMINISTRATION, WARNINGS, OVERDOSAGE**].

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 Aspirin Tablets with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). 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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see **DOSAGE AND ADMINISTRATION; Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose, WARNINGS; Life-Threatening Respiratory Depression**].

Advise both patients and caregivers about the risks of respiratory depression and sedation when Hydrocodone Bitartrate and Aspirin 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/Caregivers**].

Neonatal Opioid Withdrawal Syndrome

Use of Hydrocodone Bitartrate and Aspirin Tablets for an extended period of time 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 an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see **PRECAUTIONS; Information for Patients/Caregivers; Pregnancy**].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioids analgesics outweigh the risks of addition, abuse, and misuse, the Food and Drug Administration (FDA) has required Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Prescribers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by and accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

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

Concomitant use of Hydrocodone Bitartrate and Aspirin 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 Bitartrate and Aspirin Tablets and prolong opioid adverse reactions, and which may cause potentially fatal respiratory depression [see **WARNINGS**], particularly when an inhibitor is added after a stable dose of Hydrocodone Bitartrate and Aspirin Tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Hydrocodone Bitartrate and Aspirin Tablet-treated patients, evaluate patients at frequent intervals and consider dosage reduction of Hydrocodone Bitartrate and Aspirin Tablets until stable drug effects are achieved [see **PRECAUTIONS; Drug Interactions**].

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

Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect [see **Dependence**]. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safety switching the patient to a different opioid moiety) [see **Dosage and Administration; Warnings**].

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

The use of Hydrocodone Bitartrate and Aspirin 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 Aspirin Tablet-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 Aspirin 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**].

Regularly evaluate patients, particularly when initiating and titrating Hydrocodone Bitartrate and Aspirin Tablets and when Hydrocodone Bitartrate and Aspirin Tablets is given concomitantly with other drugs that depress respiration [see **WARNINGS; Drug Interactions**]. 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 Aspirin 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**]. Regularly evaluate these patients for signs of hypotension after initiating or titrating the dosage of Hydrocodone Bitartrate and Aspirin Tablets. In patients with circulatory shock Hydrocodone Bitartrate and Aspirin Tablets may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of Hydrocodone Bitartrate and Aspirin Tablets with circulatory shock.

Risk of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Hydrocodone Bitartrate and Aspirin Tablets may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Hydrocodone Bitartrate and Aspirin Tablets.

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

Risks of Use in Patients with Gastrointestinal Conditions

Hydrocodone Bitartrate and Aspirin Tablets are contraindicated in patients with

gastrointestinal obstruction, including paralytic ileus.

Hydrocodone may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regulatory evaluate patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Gastrointestinal Bleeding, Ulceration, and Perforation

The aspirin in Hydrocodone Bitartrate and Aspirin Tablets can cause GI side effects including stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI 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 of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For high risk such 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 Aspirin 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 **DRUG INTERACTIONS**].

Increased Risk of Seizures in Patients with Seizure Disorders

The hydrocodone in Hydrocodone Bitartrate and Aspirin 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. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during Hydrocodone Bitartrate and Aspirin Tablet therapy.

Withdrawal

Do not abruptly discontinue Hydrocodone Bitartrate and Aspirin Tablets in a patient physically dependent on opioids. When discontinuing Hydrocodone Bitartrate and Aspirin Tablets in a physically-dependent patient, gradually taper the dosage. Rapid

tapering of hydrocodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [see **DOSAGE AND ADMINISTRATION, DRUG ABUSE AND DEPENDENCE**].

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including Hydrocodone Bitartrate and Aspirin Tablets. In these patients, mixed agonist/antagonist and partial analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [see **PRECAUTIONS; Drug Interactions**].

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including Hydrocodone Bitartrate and Aspirin Tablets, in pregnant women at about 30 weeks gestation and later. NSAIDs including Hydrocodone Bitartrate and Aspirin Tablets, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including Hydrocodone Bitartrate and Aspirin Tablets, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit Hydrocodone Bitartrate and Aspirin Tablets use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if Hydrocodone Bitartrate and Aspirin Tablets treatment extends beyond 48 hours. Discontinue Hydrocodone Bitartrate and Aspirin Tablets if oligohydramnios occurs and follow up according to clinical practice [see **PRECAUTIONS; Pregnancy**].

Risks of Driving and Operating Machinery

Hydrocodone Bitartrate and Aspirin 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 Aspirin Tablets and know how they will react to the medication [see **PRECAUTIONS; Information for Patients/Caregivers**].

Hypersensitivity to Hydrocodone or Aspirin, (e.g. angioedema)

Hydrocodone Bitartrate and Aspirin Tablets are contraindicated in patients with known hypersensitivity to hydrocodone or aspirin, and in any situation where opioids or aspirin are contraindicated. Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products (NSAIDs) and in patients with the

syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

Coagulation Abnormalities and Bleeding Risks

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

Aspirin is contraindicated in patients with hemophilia.

Aspirin administered pre-operatively may prolong bleeding time.

Alcohol Warning

Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Risk of Reye's Syndrome When Used for Treatment of Viral Infections in Children or Teenagers

Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as Hydrocodone Bitartrate and Aspirin Tablets. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue Hydrocodone Bitartrate and Aspirin Tablets and evaluate the patient immediately.

PRECAUTIONS

General

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Hemorrhage

Aspirin may increase the likelihood of hemorrhage due to its effect on the gastric mucosa and platelet function (prolongation of bleeding time). Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

Ambulatory Surgery and Postoperative Use

Hydrocodone and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with use of opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

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 ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of Hydrocodone Bitartrate and Aspirin Tablets in patients with advanced renal disease. The renal effects of Hydrocodone Bitartrate and Aspirin 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 Aspirin Tablets. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Hydrocodone Bitartrate and Aspirin Tablets (see **PRECAUTIONS; Drug Interactions**). Avoid the use of Hydrocodone Bitartrate and Aspirin Tablets in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Hydrocodone Bitartrate and Aspirin Tablets is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

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

Premature Closure of Fetal Ductus Arteriosus

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

Information for Patients/Caregivers

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

Storage and Disposal

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

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

Addiction, Abuse, and Misuse

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

Life-Threatening Respiratory Depression

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

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see **WARNINGS**]. Instruct patients to take steps to store Hydrocodone Bitartrate and Aspirin Tablets securely and to dispose of unused Hydrocodone Bitartrate and Aspirin Tablets by flushing down the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if Hydrocodone Bitartrate and Aspirin Tablets are used with benzodiazepine and/or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see **WARNINGS, PRECAUTIONS; Drug Interactions**].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with Hydrocodone Bitartrate and Aspirin Tablets. Inform patients and caregivers about the

various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing regulations (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) [see **WARNINGS; Life-Threatening Respiratory Depression, DOSAGE AND ADMINISTRATION; Initial Dosage**].

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered [see **OVERDOSAGE**].

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain [see **Warnings, Adverse Reactions**].

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**].

Monoamine Oxidase Inhibitor (MAOI) Interaction

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

Important Administration Instructions

Instruct patients how to properly take Hydrocodone Bitartrate and Aspirin Tablets. The usual dosage is one or two tablets every four to six hours as needed for pain. The maximum daily dose of aspirin should not exceed 4 grams [see **DOSAGE AND ADMINISTRATION, PRECAUTIONS**].

Important Discontinuation Instructions

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

Driving or Operating Heavy Machinery

Inform patients that Hydrocodone Bitartrate and Aspirin 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**].

Constipation

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

Adrenal Insufficiency

Inform patients that the 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**].

Hypotension

Inform patients that Hydrocodone Bitartrate and Aspirin 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**].

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in Hydrocodone Bitartrate and Aspirin Tablets. Advise patients how to recognize such a reaction and when to seek medical attention [see **CONTRAINDICATIONS, ADVERSE REACTIONS**].

Serious Skin Reactions, including DRESS

Advise patients to stop taking Hydrocodone Bitartrate and Aspirin Tablets immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [see **WARNINGS**].

Aspirin Allergy

Patients should be informed that Hydrocodone Bitartrate and Aspirin Tablets contain aspirin and should not be taken by patients with an aspirin or NSAID allergy.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that the use of Hydrocodone Bitartrate and Aspirin Tablets for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see **WARNINGS, PRECAUTIONS; Pregnancy**].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that Hydrocodone Bitartrate and Aspirin Tablets can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy. Avoid use of Hydrocodone Bitartrate and Aspirin Tablets and

other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [see **WARNINGS; Premature Closure of the Ductus Arteriosus, PRECAUTIONS; Pregnancy**].

Inform pregnant women to avoid use of aspirin and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with Hydrocodone Bitartrate and Aspirin Tablets is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [see **WARNINGS; Fetal Toxicity, PRECAUTIONS; Pregnancy**].

Lactation

Advise nursing mothers to carefully observe 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 (Lactation)**].

Infertility

Inform patients that use of opioids for extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible [see **ADVERSE REACTIONS**]. Advise females of reproductive potential who desire pregnancy that NSAIDs, including Hydrocodone Bitartrate and Aspirin Tablets, may be associated with a reversible delay in ovulation [see **Use in Specific Populations (PRECAUTIONS; Carcinogenesis, Mutagenesis, Impairment of Fertility)**].

Risk of Bleeding

Inform patients about the signs and symptoms of bleeding. Tell patients to notify their physician if they are prescribed any drug which may increase risk of bleeding.

Counsel patients who consume three or more alcoholic drinks daily about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin [see **WARNINGS**].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of Hydrocodone Bitartrate and Aspirin Tablets with NSAIDs or other 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, PRECAUTIONS; Drug Interactions**]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Laboratory Tests

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time. In patients with severe hepatic or renal disease, effects of therapy should be followed with serial liver and/or renal function tests.

Hypersensitivity to aspirin cannot be detected by skin testing or radioimmunoassay procedure.

Drug Interactions

Table 1: Clinically Significant Drug Interactions with Hydrocodone Bitartrate and Aspirin Tablets

Inhibitors of CYP3A4 and CYP2D6	
<i>Clinical Impact:</i>	The concomitant use of Hydrocodone Bitartrate and Aspirin Tablets and CYP3A4 inhibitors 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 Aspirin Tablets and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of Hydrocodone Bitartrate and Aspirin Tablets is achieved [see WARNINGS]. After stopping CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone plasma concentration will decrease [see CLINICAL PHARMACOLOGY], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to hydrocodone.
<i>Intervention:</i>	If concomitant use is necessary, consider dosage reduction of Hydrocodone Bitartrate and Aspirin Tablets until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the Hydrocodone Bitartrate and Aspirin Tablets dosage until stable drug effects are achieved. Evaluate for signs of opioid withdrawal.
<i>Examples:</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
<i>Clinical Impact:</i>	The concomitant use of Hydrocodone Bitartrate and Aspirin Tablets and CYP3A4 inducers can decrease the plasma concentration of hydrocodone [see CLINICAL PHARMACOLOGY], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to hydrocodone [see WARNINGS]. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone plasma concentration will increase [see CLINICAL PHARMACOLOGY], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the Hydrocodone Bitartrate and Aspirin Tablets dosage until stable drug effects are achieved. Evaluate for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider Hydrocodone Bitartrate and Aspirin Tablets dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation.
<i>Examples:</i>	Rifampin, carbamazepine, phenytoin
Benzodiazepines and other Central Nervous System (CNS) Depressants	

<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	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. Inform patients and caregivers of this potential interaction, educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see WARNINGS].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

Serotonergic Drugs

<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue Hydrocodone Bitartrate and Aspirin Tablets if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (<i>i.e.</i> , cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Monoamine Oxidase Inhibitors (MAOIs)

<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see WARNINGS].
<i>Intervention:</i>	The use of Hydrocodone Bitartrate and Aspirin Tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely evaluating blood pressure and signs and symptoms of CNS and respiratory depression.
<i>Examples:</i>	Phenelzine, tranylcypromine, linezolid

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

<i>Clinical Impact:</i>	May reduce the analgesic effect of Hydrocodone Bitartrate and Aspirin Tablets and/or precipitate withdrawal symptoms
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	Butorphanol, nalbuphine, pentazocine, buprenorphine

Muscle Relaxants	
<i>Clinical Impact:</i>	Hydrocodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Because respiratory depression may be greater than otherwise expected, decrease the dosage of Hydrocodone Bitartrate and Aspirin Tablets and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose.
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.
<i>Intervention:</i>	Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Evaluate patients for signs of urinary retention or reduced gastric motility when Hydrocodone Bitartrate and Aspirin Tablets is used concomitantly with anticholinergic drugs.
Anticoagulants	
<i>Clinical Impact:</i>	Aspirin may enhance the effects of anticoagulants. Concurrent use may increase the risk of bleeding. Aspirin can also displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time.
<i>Intervention:</i>	Follow patients for signs of bleeding.
<i>Examples:</i>	Warfarin, heparin, enoxaparin, clopidogrel, prasugrel, rivaroxaban, apixaban
Uricosuric Agents	
<i>Clinical Impact:</i>	Aspirin inhibits the uricosuric effects of uricosuric agents.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	Probenecid
Carbonic Anhydrase Inhibitors	
<i>Clinical Impact:</i>	Concurrent use with aspirin can lead to high serum concentrations of the carbonic anhydrase inhibitor and cause toxicity due to competition at the renal tubule for secretion.
<i>Intervention:</i>	Consider reducing the dose of the carbonic anhydrase inhibitor and follow patient for any adverse effects from the carbonic anhydrase inhibitor.

<i>Examples:</i>	Acetazolamide, methazolamide
Methotrexate	
<i>Clinical Impact:</i>	Aspirin may enhance the toxicity of methotrexate by displacing it from its plasma protein binding sites and/or reducing its renal clearance.
<i>Intervention:</i>	Use caution if using concomitantly, especially in elderly patients or patients with renal impairment. Follow patients for methotrexate toxicity.
Nephrotoxic Agents	
<i>Clinical Impact:</i>	Concomitant use with aspirin may lead to additive nephrotoxicity due to the inhibition of renal prostaglandins by aspirin. Also, the plasma concentration of aspirin is increased by conditions that reduce the glomerular filtration rate or tubular secretion.
<i>Intervention:</i>	Use Hydrocodone Bitartrate and Aspirin Tablets with caution if used concomitantly with nephrotoxic agents. Closely follow the renal function of patients.
<i>Examples:</i>	Aminoglycosides, amphotericin B, systemic bacitracin, cisplatin, cyclosporine, foscarnet, or parenteral vancomycin
Angiotensin Converting Enzyme (ACE) Inhibitors	
<i>Clinical Impact:</i>	The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.
<i>Intervention:</i>	Use caution if using concomitantly. Follow the blood pressure and renal function of patients.
<i>Examples:</i>	Ramipril, captopril
Beta Blockers	
<i>Clinical Impact:</i>	The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.
<i>Intervention:</i>	Use caution if using concomitantly. Follow the blood pressure and renal function of patients.
<i>Examples:</i>	Metoprolol, propranolol
Hypoglycemic Agents	
<i>Clinical Impact:</i>	Aspirin may increase the serum glucose-lowering action of insulin and sulfonylureas leading to hypoglycemia.
<i>Intervention:</i>	Patients should be advised to consult a physician if any signs or symptoms of hypoglycemia occur.
<i>Examples:</i>	Insulin, glimepiride, glipizide
Anticonvulsants	
<i>Clinical Impact:</i>	Aspirin can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.
<i>Intervention:</i>	Use caution if using concomitantly.
<i>Examples:</i>	Phenytoin, valproic acid
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	

<i>Clinical Impact:</i>	Concurrent use of aspirin with other NSAIDs may increase the risk of bleeding or lead to decreased renal function. Aspirin may enhance serious side effects and toxicity of ketorolac by displacing it from its plasma protein binding sites and/or reducing its renal clearance.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	Ketorolac, ibuprofen, naproxen, diclofenac
Corticosteroids	
<i>Clinical Impact:</i>	In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.
<i>Intervention:</i>	Avoid concomitant use.

Drug/Laboratory Test Interactions

Depending on the sensitivity/specificity and the test methodology, the individual components of Hydrocodone Bitartrate and Aspirin Tablets may cross-react with assays used in the preliminary detection of cocaine (primary urinary metabolite, benzoylecgonine) or marijuana (cannabinoids) in human urine. A more specific alternate chemical method must be used in order to obtain a confirmed analytical result. The preferred confirmatory method is gas chromatography/mass spectrometry (GC/MS). Moreover, clinical considerations and professional judgment should be applied to any drug-of-abuse test result, particularly when preliminary positive results are used.

Salicylates may increase the protein bound iodine (PBI) result by competing for the protein binding sites on pre-albumin and possibly thyroid-binding globulins.

Aspirin

Aspirin may interfere with the following laboratory determinations:

In blood: serum amylase, fasting blood glucose, carbon dioxide, cholesterol, protein, protein bound iodine, uric acid, prothrombin time, bleeding time, and spectrophotometric detection of barbiturates.

In urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), protein, uric acid, and diacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies to evaluate the carcinogenic potential of the combination of Hydrocodone Bitartrate and Aspirin Tablets have not been conducted.

Administration of aspirin for 68 weeks at 0.5 percent in the feed of rats was not carcinogenic.

Mutagenesis

The combination of hydrocodone and aspirin has not been evaluated for mutagenicity. In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce

chromosome aberrations in cultured human fibroblasts.

Impairment of Fertility

Animal studies to evaluate the effects of hydrocodone on fertility have not been conducted. Aspirin has been shown to inhibit ovulation in rats.

Pregnancy

Risk Summary

Use of NSAIDs, including aspirin, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of Hydrocodone Bitartrate and Aspirin Tablets use between about 20 weeks of gestation, and avoid Hydrocodone Bitartrate and Aspirin Tablets use at about 30 weeks of gestation and later in pregnancy [see **WARNINGS; Fetal Toxicity**].

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including aspirin, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

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 aspirin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) 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

Use of opioid analgesics for an extended period of time 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, 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**].

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including Hydrocodone Bitartrate and Aspirin Tablets, can cause premature closure of the fetal ductus arteriosus [see **WARNINGS; Fetal Toxicity**].

Oligohydramnios/Neonatal Renal Impairment

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If Hydrocodone Bitartrate and Aspirin Tablets treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue Hydrocodone Bitartrate and Aspirin Tablets and follow up according to clinical practice [see **WARNINGS; Fetal Toxicity**].

Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. An opioid antagonist, such as naloxone must be available for reversal of opioid-induced respiratory depression in the neonate. Hydrocodone Bitartrate and Aspirin Tablets is 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. Occasionally, opioid analgesics, including Hydrocodone Bitartrate and Aspirin Tablets, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Aspirin should be avoided one week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some which were

irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

Animal reproduction studies with the combination of hydrocodone and aspirin or the individual drugs alone are not available.

Lactation

Risk Summary

Hydrocodone is present in human milk.

Salicylic acid has been detected in breast milk. Adverse effects on platelet function in the nursing infant exposed to aspirin in breast milk may be a potential risk. Furthermore, the risk of Reye's Syndrome caused by salicylate in breast milk is unknown.

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

Clinical Considerations

Monitor infants exposed to Hydrocodone Bitartrate and Aspirin Tablets through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

Females and Males of Reproductive Potential

Infertility

Use of opioids for extended period of time 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**].

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including aspirin, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including aspirin, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Pediatric Use

Hydrocodone Bitartrate and Aspirin Tablets should not be administered to pediatric patients. Reye's Syndrome is a rare but serious disease which can follow flu or chicken pox in children and teenagers. While the cause of Reye's Syndrome is unknown, some reports claim aspirin (or salicylates) may increase the risk of developing this disease.

Geriatric Use

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

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

Hydrocodone and aspirin 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 regularly evaluate renal function.

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, dose selection should start at the low end of the dosing range, and follow patients for adverse effects [see **WARNINGS, PRECAUTIONS**].

Hepatic Impairment

Patients with hepatic impairment may have higher plasma hydrocodone concentrations than those with normal function. Use a low initial dose of Hydrocodone Bitartrate and Aspirin Tablets in patients with hepatic impairment and follow closely for adverse events such as respiratory depression and sedation.

Avoid aspirin in patients with severe hepatic impairment.

Renal Impairment

Patients with renal impairment may have higher plasma hydrocodone concentrations than those with normal function. Use a low initial dose Hydrocodone Bitartrate and Aspirin Tablets in patients with renal impairment and follow closely for adverse events such as respiratory depression and sedation.

Avoid aspirin in patients with severe renal impairment (glomerular filtration rate less than 10 mL/minute).

ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse [see **WARNINGS**]
- Life-Threatening Respiratory Depression [see **WARNINGS**]
- Interactions with Benzodiazepines and Other CNS Depressants [see **WARNINGS**]
- Neonatal Opioid Withdrawal Syndrome [see **WARNINGS**]
- Opioid-Induced Hyperalgesia and Allodynia [see **WARNINGS**]
- Adrenal Insufficiency [see **WARNINGS**]
- Severe Hypotension [see **WARNINGS**]
- Gastrointestinal Adverse Reactions [see **WARNINGS**]
- Seizures [see **WARNINGS**]
- Withdrawal [see **WARNINGS**]
- Coagulation Abnormalities and Bleeding [see **WARNINGS**]
- Reye's Syndrome [see **WARNINGS**]
- Renal Toxicity and Hyperkalemia [see **PRECAUTIONS**]
- Premature Closure of the Fetal Ductus Arteriosus [see **PRECAUTIONS**]

Postmarketing Experience

The following adverse reactions associated with the use of Hydrocodone Bitartrate and Aspirin Tablets were identified in clinical studies or postmarketing reports. Because some of these reactions were 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.

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature [see **WARNINGS**].

Body as a Whole: Fever, hypothermia, thirst.

Cardiovascular: Dysrhythmias, hypotension, tachycardia.

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.

Fluid and Electrolyte: Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's Syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.

Hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

Musculoskeletal: Rhabdomyolysis.

Metabolism: Hypoglycemia (in children), hyperglycemia.

Reproductive: Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

Respiratory: Hyperpnea, pulmonary edema, tachypnea.

Special Senses: Hearing loss, tinnitus. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

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 Aspirin Tablets.

Androgen deficiency: Cases of androgen deficiency have with use of opioids for an extended period of time [see **CLINICAL PHARMACOLOGY**].

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration [see **WARNINGS**].

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

To report SUSPECTED ADVERSE REACTIONS, contact LGM Pharma Solutions, LLC at 1-877-288-1495 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Hydrocodone Bitartrate and Aspirin Tablets contain hydrocodone, a Schedule II controlled substance.

Abuse

Hydrocodone Bitartrate and Aspirin Tablets contain hydrocodone, a substance with a high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction [see **WARNINGS**].

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of Hydrocodone Bitartrate and Aspirin Tablets increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of Hydrocodone Bitartrate and Aspirin Tablets with alcohol and other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of Hydrocodone Bitartrate and Aspirin Tablets abuse include those with a history of prolonged use of any opioid, including products containing hydrocodone, those with a history of drug or alcohol abuse, or those who use Hydrocodone Bitartrate and Aspirin Tablets in combination with other abused drugs.

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

Hydrocodone Bitartrate and Aspirin Tablets, like other opioids, can be diverted for nonmedical 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 reevaluation 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 Aspirin Tablets

Abuse of Hydrocodone Bitartrate and Aspirin Tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of Hydrocodone Bitartrate and Aspirin Tablets with alcohol and/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 use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), 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 use.

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

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

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

OVERDOSAGE

Clinical Presentation

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

Early signs of acute aspirin (salicylate) overdose including tinnitus occur at plasma concentrations approaching 200 mcg/mL. Plasma concentrations of aspirin above 300 mcg/mL are toxic. Severe toxic effects are associated with levels above 400 mcg/mL. A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately.

In acute salicylate overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration, and coma. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis. Serious symptoms such as depression, coma, and respiratory failure progress rapidly.

Salicylism (chronic salicylate toxicity) may be noted by symptoms such as dizziness, tinnitus, difficulty hearing, nausea, vomiting, diarrhea, and mental confusion. More

severe salicylism may result in respiratory alkalosis.

Treatment of Overdose

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

Opioid antagonists, such as naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary opioid overdose, administer an opioid antagonist. Because the duration of opioid reversal is expected to be less than the duration of action of hydrocodone in Hydrocodone Bitartrate and Aspirin Tablets, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of the 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.

In severe cases of salicylate overdose, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia. With more severe acute toxicity respiratory alkalosis may occur.

Hemodialysis and peritoneal dialysis can be performed to reduce the body content of aspirin. In patients with renal insufficiency or in cases of life-threatening salicylate intoxication dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions

Hydrocodone Bitartrate and Aspirin Tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.

Use the lowest effective dosage for the shortest duration of time consistent with the individual patient treatment goals [see **WARNINGS**]. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of Hydrocodone Bitartrate with Aspirin Tablets for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using higher dose opioid clearly outweigh the substantial risks.

Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.

There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addition, abuse, and misuse [see **WARNINGS**].

Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increase with Hydrocodone Bitartrate and Aspirin Tablets. Consider the risk when selecting an initial dose and when making dose adjustments [see **WARNINGS**]. Administer Hydrocodone Bitartrate and Aspirin Tablets with food or a full glass of water to minimize GI distress.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Hydrocodone Bitartrate and Aspirin Tablets [see **WARNINGS; Life-Threatening Respiratory Depression, PRECAUTIONS; Information for Patients/Caregivers**].
- Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient [see **WARNINGS; Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Life-Threatening Respiratory Depression; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**].
- Consider prescribing naloxone when there are household members (including children) or other close contacts at risk for accidental ingestion or overdose.

Initial Dosage

Initiating Treatment with Hydrocodone Bitartrate and Aspirin Tablets

Initiate treatment with Hydrocodone Bitartrate and Aspirin Tablets using one (1) or two (2) tablets every four (4) to six (6) hours, as needed for pain at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of Hydrocodone Bitartrate and Aspirin Tablets.

Conversion from Other Opioids to Hydrocodone Bitartrate and Aspirin Tablets

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of Hydrocodone Bitartrate and Aspirin Tablets. It is safer to underestimate a patient's

24-hour Hydrocodone Bitartrate and Aspirin Tablets dosage than to overestimate the 24-hour Hydrocodone Bitartrate and Aspirin Tablets dosage and manage an adverse reaction due to an overdose.

Conversion from Hydrocodone Bitartrate and Aspirin Tablets to Extended-Release Hydrocodone

The relative bioavailability of Hydrocodone Bitartrate and Aspirin Tablets compared to extended-release hydrocodone is unknown, so conversion to extended-release hydrocodone may lead to increased risk of excessive sedation and respiratory depression.

Titration and Maintenance of Therapy

Individually titrate Hydrocodone Bitartrate and Aspirin Tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Hydrocodone Bitartrate and Aspirin Tablets to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as reassess for the development of addiction, abuse, or misuse [see **WARNINGS**]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of the increased pain before increasing the Hydrocodone Bitartrate and Aspirin Tablets dosage. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after dosage increase), consider reducing the dosage [see **WARNINGS**]. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Safe Reduction or Discontinuation of Hydrocodone Bitartrate and Aspirin Tablets

Do not abruptly discontinue Hydrocodone Bitartrate and Aspirin Tablets in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

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

benefit from referral to a specialist.

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

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

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

HOW SUPPLIED

Hydrocodone Bitartrate and Aspirin Tablets are supplied as oval, bisected white tablets containing 5 mg Hydrocodone Bitartrate and 500 mg of Aspirin. Each tablet is debossed with “MLB” bisect “125” on one side and “5-500” on the other side.

Bottles of 100 tablets – NDC 79739-7182-1

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

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

Protect from moisture.

Store Hydrocodone Bitartrate and Aspirin Tablets securely and dispose of properly [see **PRECAUTIONS; Information for Patients/Caregivers**]

Manufactured by: LGM Pharma Solutions, LLC, Irvine, CA 92614

7182-PD

Rev 01/2024

Medication Guide

Hydrocodone Bitartrate (hye'' droe koe' done bye tar' trate) and **Aspirin** (as' pir in) **Tablets CII**

Hydrocodone Bitartrate and Aspirin Tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require an opioid pain medicine, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about Hydrocodone Bitartrate and Aspirin Tablets:

- **Get emergency help right away or call 911 if you take too much Hydrocodone Bitartrate and Aspirin Tablets (overdose).** When you first start taking Hydrocodone Bitartrate and Aspirin Tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking Hydrocodone Bitartrate and Aspirin 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 Aspirin Tablets. They could die from taking it. Selling or giving away Hydrocodone Bitartrate and Aspirin Tablets is against the law.
- Store Hydrocodone Bitartrate and Aspirin Tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
- Increases risk of bleeding and ulcers.

Do not take Hydrocodone Bitartrate and Aspirin Tablets if you have:

- severe asthma, asthma in combination with runny nose and nasal polyps, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- known hypersensitivity to hydrocodone or aspirin, or any ingredient in Hydrocodone Bitartrate and Aspirin Tablets.
- known allergy to nonsteroidal anti-inflammatory drug products (NSAIDs)
- a rare disorder in which your blood doesn't clot normally (hemophilia)

Do not give Hydrocodone Bitartrate and Aspirin Tablets to a child or teenager with a viral illness. Reye's syndrome, a life-threatening condition, can happen when aspirin (an ingredient in Hydrocodone Bitartrate and Aspirin Tablets) is used in children and teenagers who have certain viral illnesses.

Before taking Hydrocodone Bitartrate and Aspirin Tablets, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems

- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.
- stomach ulcers, or stomach or intestinal bleeding with use of acetylsalicylic acid (ASA) or NSAIDs

Tell your healthcare provider if you are:

- noticing your pain getting worse. If your pain gets worse after you take Hydrocodone Bitartrate and Aspirin Tablets, do not take more of Hydrocodone Bitartrate and Aspirin Tablets without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking Hydrocodone Bitartrate and Aspirin Tablets.
- **pregnant or planning to become pregnant.** Use of Hydrocodone Bitartrate and Aspirin Tablets for extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Taking NSAID-containing products like Hydrocodone Bitartrate and Aspirin Tablets at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- **breastfeeding.** Hydrocodone bitartrate and aspirin passes into breast milk and may harm your baby. Carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Seek immediate medical care if you notice these signs.
- **develop any type of rash or fever.** Contact your healthcare provider as soon as possible and stop taking Hydrocodone Bitartrate and Aspirin Tablets.
- living in a household where there are small children or someone who has abused street or prescription drugs
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking Hydrocodone Bitartrate and Aspirin Tablets with certain other medicines can cause serious side effects that could lead to death. Taking with corticosteroids or anticoagulants increases risk of ulcers and stomach/intestinal bleeding.

When taking Hydrocodone Bitartrate and Aspirin Tablets:

- Do not change your dose. Take Hydrocodone Bitartrate and Aspirin Tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- For acute (short-term) pain, you may only need to take Hydrocodone Bitartrate and Aspirin Tablets for a few days. You may have some Hydrocodone Bitartrate and Aspirin Tablets left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused Hydrocodone Bitartrate and Aspirin Tablets.
- Take your prescribed dose every four to six hours as needed for pain.
- Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking Hydrocodone Bitartrate and Aspirin Tablets regularly, do not

stop taking Hydrocodone Bitartrate and Aspirin Tablets without talking to your healthcare provider.

- Dispose of expired, unwanted, or unused Hydrocodone Bitartrate and Aspirin Tablets by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking Hydrocodone Bitartrate and Aspirin Tablets DO NOT:

- Drive or operate heavy machinery, until you know how Hydrocodone Bitartrate and Aspirin Tablets affects you. Hydrocodone Bitartrate and Aspirin 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 Aspirin Tablets may cause you to overdose and die.

The possible side effects of Hydrocodone Bitartrate and Aspirin Tablets:

- Bleeding, constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, rash, or fever. Call your healthcare provider if you have any of these symptoms and they are severe.
- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

Get emergency medical help or call 911 right away if you have:

These are not all the possible side effects of Hydrocodone Bitartrate and Aspirin Tablets. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov.**

Manufactured by:
LGM Pharma Solutions, LLC
Irvine, CA 92614

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

7182-PD

Issued: 01/2024

PRINCIPAL DISPLAY PANEL

NDC 79739-7182-1

Hydrocodone Bitartrate and Aspirin Tablets CIII

5 mg/500 mg

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

Rx only

100 TABLETS

Manufactured by : LGM Pharma Solutions, LLC

Irvine, CA 92614

EACH TABLET CONTAINS:

Hydrocodone Bitartrate 5 mg
Aspirin..... 500 mg

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

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

Protect from moisture.

7182-PD

Rev 05/2021

The usual adult dosage is one or two tablets every four to six hours as needed for pain.

KEEP OUT OF THE REACH OF CHILDREN.



HYDROCODONE BITARTRATE AND ASPIRIN

hydrocodone bitartrate and aspirin tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:79739-7182
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	5 mg
ASPIRIN (UNII: R16CO5Y76E) (ASPIRIN - UNII:R16CO5Y76E)	ASPIRIN	500 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
HYDROXYPROPYL CELLULOSE (90000 WAMW) (UNII: UKE75GEA7F)	
CROSPROVIDONE (12 MPA.S AT 5%) (UNII: 40UAA97IT9)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	white	Score	2 pieces
Shape	OVAL	Size	17mm
Flavor		Imprint Code	MLB;125;5;500
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:79739-7182-1	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/28/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205479	05/28/2021	

Labeler - LGM PHARMA SOLUTIONS, LLC (117549198)

Revised: 3/2024

LGM PHARMA SOLUTIONS, LLC