HYDROCODONE BITARTRATE AND ACETAMINOPHEN- hydrocodone bitartrate and acetaminophen tablet
Direct Rx

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

Hydrocodone bitartrate and acetaminophen, USP is available in tablet form for oral administration.
Hydrocodone bitartrate is an opioid analgesic and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:
Hydrocodone Bitartrate- Struct
Acetaminophen, 4' -hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:
Acetaminophen- Struct
Each Hydrocodone Bitartrate and Acetaminophen Tablet, USP contains:

Strength	Hydrocodone Bitartrate	Acetaminophen
5 mg/325 mg	5 mg	325 mg
10 mg/325 mg	10 mg	325 mg

In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, corn starch, colloidal silicon dioxide, crospovidone, pregelatinized starch, povidone, and stearic acid.
Hydrocodone Bitartrate and Acetaminophen Tablets, USP complies to USP Dissolution Test 1.

Mechanism of Action

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

Pharmacodynamics

Effects on the Central Nervous System

The principal therapeutic action of hydrocodone is analgesia. 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.

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

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Hydrocodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

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

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see ADVERSE REACTIONS].

Effects on the Immune System

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

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see DOSAGE AND ADMINISTRATION].

Concentration-Adverse Reaction Relationships

There is a relationship between increasing hydrocodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see DOSAGE AND ADMINISTRATION].

Pharmacokinetics

The behavior of the individual components is described below.

Hydrocodone

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.

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. See OVERDOSAGE for toxicity information.

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. Hydrocodone and its metabolites are eliminated primarily in the kidneys.

Acetaminophen

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

See OVERDOSAGE for toxicity information.

Hydrocodone bitartrate and acetaminophen tablets, USP are indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, even at

recommended doses [see WARNINGS], reserve hydrocodone bitartrate and acetaminophen tablets, USP 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

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

The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychological dependence, mood changes.

Gastrointestinal System: Constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters, and urinary retention.

Special Senses: Cases of hearing impairment or permanent loss have been reported predominately in patients with chronic overdose.

Dermatological: Skin rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, allergic reactions.

Hematological: Thrombocytopenia, agranulocytosis.

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 acetaminophen tablets.
Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see CLINICAL PHARMACOLOGY].

Controlled Substance

Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, a Schedule II controlled substance.

Abuse

Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, a substance with a high potential for abuse similar to other opioids, including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol, can be abused and are subject to misuse, addiction, and criminal diversion [see WARNINGS].

All patients treated with opioids require careful monitoring for signs of abuse and

addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

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

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

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

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

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

Risks Specific to Abuse of Hydrocodone Bitartrate and Acetaminophen Tablets

Hydrocodone bitartrate and acetaminophen tablets are for oral use only. Hydrocodone bitartrate and acetaminophen tablets pose a risk of overdose and death. The risk is increased with concurrent abuse of hydrocodone bitartrate and acetaminophen tablets with alcohol and other central nervous system depressants.

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

Dependence

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

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt

discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue hydrocodone bitartrate and acetaminophen tablets in a patient physically dependent on opioids. Rapid tapering of hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets, gradually taper the dosage using a patient specific plan that considers the following: the dose of hydrocodone bitartrate and acetaminophen tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [see DOSAGE AND ADMINISTRATION, WARNINGS].

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

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Clinical Presentation

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

Acetaminophen

Dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect of acetaminophen overdosage. Renal tubular necrosis, hypoglycemic coma and coagulation defects may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment of Overdose

Hydrocodone

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive

measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to 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 acetaminophen tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

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

Acetaminophen

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

Important Dosage and Administration Instructions
Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see WARNINGS].
Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see WARNINGS].
Follow patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with hydrocodone bitartrate and acetaminophen tablets and adjust the dosage accordingly [see WARNINGS].
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 acetaminophen 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 regulations (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).
Consider prescribing naloxone, based on the patients 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, Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants].
Consider prescribing naloxone when the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.
Initial Dosage
Initiating Treatment with Hydrocodone Bitartrate and Acetaminophen Tablets
2.5 mg/325 mg The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.
5 mg/325 mg The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.
7.5 mg/325 mg,
10 mg/325 mg
The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
Conversion from Other Opioids to Hydrocodone Bitartrate and Acetaminophen 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 acetaminophen tablets. It is safer to underestimate a patient’s 24-hour hydrocodone bitartrate and acetaminophen tablets dosage than to overestimate the 24-hour hydrocodone bitartrate and acetaminophen tablets dosage and manage an adverse reaction due to overdose.
Conversion from Hydrocodone Bitartrate and Acetaminophen Tablets to Extended-Release Hydrocodone
The relative bioavailability of hydrocodone from hydrocodone bitartrate and acetaminophen tablets compared to extended-release hydrocodone products is unknown, so conversion to extended-release products must be accompanied by close observation for signs of excessive sedation and respiratory depression.
Titration and Maintenance of Therapy
Individually titrate hydrocodone bitartrate and acetaminophen tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving hydrocodone bitartrate and acetaminophen tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see WARNINGS].
Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.
If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the hydrocodone bitartrate and acetaminophen tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.
Safe Reduction or Discontinuation of Hydrocodone Bitartrate and Acetaminophen

Tablets

Do not abruptly discontinue hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets, there are a variety of factors that should be considered, including the dose of hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

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

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

Hydrocodone Bitartrate and Acetaminophen Tablets, USP are supplied as

5 mg/325 mg

containing 5 mg hydrocodone bitartrate and 325 mg acetaminophen. Off white/white capsule shaped tablet debossed ‘T 257’ on one side and plain on other side with bisect line.

Bottles of 100 Tablets

Bottles of 500 Tablets

10 mg/325 mg

containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen. Off white/white capsule shaped tablet debossed ‘T 259’ on one side and plain on other side with bisect line.

Bottles of 100 Tablets

Bottles of 500 Tablets

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

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

Store hydrocodone bitartrate and acetaminophen tablets securely and dispose of properly [see PRECAUTIONS/Information for Patients].

Manufactured by:

Ascent Pharmaceuticals, Inc.

Central Islip, NY 11722

Manufactured for:

Camber Pharmaceuticals, Inc.

Piscataway, NJ 08854

Revised: 05/21

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Addiction, Abuse, and Misuse: RISK EVALUATION AND MITIGATION STRATEGY (REMS)
Hydrocodone bitartrate and acetaminophen tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk prior to prescribing hydrocodone bitartrate and acetaminophen tablets, and monitor all patients regularly for the development of these behaviors and conditions [see WARNINGS].
Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see WARNINGS]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to complete a REMS-compliant education program,
counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
consider other tools to improve patient, household, and community safety.
Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of hydrocodone bitartrate and acetaminophen tablets. Monitor for respiratory depression especially during initiation of hydrocodone bitartrate and acetaminophen tablets or following a dose increase [see WARNINGS].
Accidental Ingestion
Accidental ingestion of hydrocodone bitartrate and acetaminophen tablets, especially by children, can result in a fatal overdose of hydrocodone bitartrate and acetaminophen tablets [see WARNINGS].
Neonatal Opioid Withdrawal Syndrome
Prolonged use of hydrocodone bitartrate and acetaminophen tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant

woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see WARNINGS].

Cytochrome P450 3A4 Interaction

The concomitant use of hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets and any cytochrome P450 3A4 inhibitor or inducer for signs of respiratory depression or sedation [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product [see WARNINGS, OVERDOSAGE].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see WARNINGS, PRECAUTIONS; Drug Interactions].

Reserve concomitant prescribing of hydrocodone bitartrate and acetaminophen tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

CLOSE

DESCRIPTION

Hydrocodone bitartrate and acetaminophen, USP is available in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Hydrocodone Bitartrate- Struct

Acetaminophen, 4' -hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

Acetaminophen- Struct

Each Hydrocodone Bitartrate and Acetaminophen Tablet, USP contains:

Strength	Hydrocodone Bitartrate	Acetaminophen
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In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, corn starch, colloidal silicon dioxide, crospovidone, pregelatinized starch, povidone, and stearic acid.

Hydrocodone Bitartrate and Acetaminophen Tablets, USP complies to USP Dissolution Test 1.

CLOSE

CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

Effects on the Central Nervous System

The principal therapeutic action of hydrocodone is analgesia. 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.

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

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Hydrocodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

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

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see ADVERSE REACTIONS].

Effects on the Immune System

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

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see DOSAGE AND ADMINISTRATION].

Concentration-Adverse Reaction Relationships

There is a relationship between increasing hydrocodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see DOSAGE AND ADMINISTRATION].

Pharmacokinetics

The behavior of the individual components is described below.

Hydrocodone

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. 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. See OVERDOSAGE for toxicity information.

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. Hydrocodone and its metabolites are eliminated primarily in the kidneys.

Acetaminophen

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. A small fraction (10-25%) of acetaminophen is bound to plasma proteins. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

CLOSE
INDICATIONS AND USAGE
Hydrocodone bitartrate and acetaminophen tablets, USP are indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Limitations of Use
Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see WARNINGS], reserve hydrocodone bitartrate and acetaminophen tablets, USP 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
CLOSE
CONTRAINDICATIONS
Hydrocodone bitartrate and acetaminophen tablets are contraindicated in patients with: Significant respiratory depression [see WARNINGS] Acute or severe bronchial asthma in an unmonitored setting ...
WARNINGS
Addiction, Abuse, and Misuse - Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, a Schedule II controlled substance. As an opioid, hydrocodone bitartrate and acetaminophen ...
PRECAUTIONS
Risks of Driving and Operating Machinery - Hydrocodone bitartrate and acetaminophen tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as ...
ADVERSE REACTIONS
The following adverse reactions have been identified during post approval use of hydrocodone and acetaminophen tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting.
Other adverse reactions include:
Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychological dependence, mood changes.
Gastrointestinal System: Constipation.
Genitourinary System: Ureteral spasm, spasm of vesical sphincters, and urinary retention.
Special Senses: Cases of hearing impairment or permanent loss have been reported predominately in patients with chronic overdose.
Dermatological: Skin rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, allergic reactions.
Hematological: Thrombocytopenia, agranulocytosis.
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 acetaminophen tablets.
Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see CLINICAL PHARMACOLOGY].
CLOSE
DRUG ABUSE AND DEPENDENCE
Controlled Substance
Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, a Schedule II controlled substance.
Abuse
Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, a substance with a high potential for abuse similar to other opioids, including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol, can be abused and are subject to misuse, addiction, and criminal diversion [see WARNINGS].
All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.
Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.
“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.
Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.
Hydrocodone bitartrate and acetaminophen tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.
Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.
Risks Specific to Abuse of Hydrocodone Bitartrate and Acetaminophen Tablets
Hydrocodone bitartrate and acetaminophen tablets are for oral use only. Hydrocodone bitartrate and acetaminophen tablets pose a risk of overdose and death. The risk is increased with concurrent abuse of hydrocodone bitartrate and acetaminophen tablets with alcohol and other central nervous system depressants.
Parenteral drug abuse is commonly associated with transmission of infectious diseases

such as hepatitis and HIV.

Dependence

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

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue hydrocodone bitartrate and acetaminophen tablets in a patient physically dependent on opioids. Rapid tapering of hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets, gradually taper the dosage using a patient specific plan that considers the following: the dose of hydrocodone bitartrate and acetaminophen tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [see DOSAGE AND ADMINISTRATION, WARNINGS].

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

CLOSE

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Clinical Presentation

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

Acetaminophen

Dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect of acetaminophen overdosage. Renal tubular necrosis, hypoglycemic coma and coagulation defects may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic

toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment of Overdose

Hydrocodone

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

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to 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 acetaminophen tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product’s prescribing information.

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

Acetaminophen

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

CLOSE

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see WARNINGS].

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

Follow patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with hydrocodone bitartrate and acetaminophen tablets and adjust the dosage accordingly [see WARNINGS].

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 acetaminophen 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 regulations (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).
Consider prescribing naloxone, based on the patients 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, Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants].
Consider prescribing naloxone when the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.
Initial Dosage
Initiating Treatment with Hydrocodone Bitartrate and Acetaminophen Tablets
2.5 mg/325 mg The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.
5 mg/325 mg The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.
7.5 mg/325 mg,
10 mg/325 mg
The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
Conversion from Other Opioids to Hydrocodone Bitartrate and Acetaminophen 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 acetaminophen tablets. It is safer to underestimate a patient’s 24-hour hydrocodone bitartrate and acetaminophen tablets dosage than to overestimate the 24-hour hydrocodone bitartrate and acetaminophen tablets dosage and manage an adverse reaction due to overdose.
Conversion from Hydrocodone Bitartrate and Acetaminophen Tablets to Extended-Release Hydrocodone
The relative bioavailability of hydrocodone from hydrocodone bitartrate and acetaminophen tablets compared to extended-release hydrocodone products is unknown, so conversion to extended-release products must be accompanied by close observation for signs of excessive sedation and respiratory depression.
Titration and Maintenance of Therapy
Individually titrate hydrocodone bitartrate and acetaminophen tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving hydrocodone bitartrate and acetaminophen tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see WARNINGS].
Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.
If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the hydrocodone bitartrate and acetaminophen tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between

management of pain and opioid-related adverse reactions.

Safe Reduction or Discontinuation of Hydrocodone Bitartrate and Acetaminophen Tablets

Do not abruptly discontinue hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets, there are a variety of factors that should be considered, including the dose of hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

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

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

CLOSE

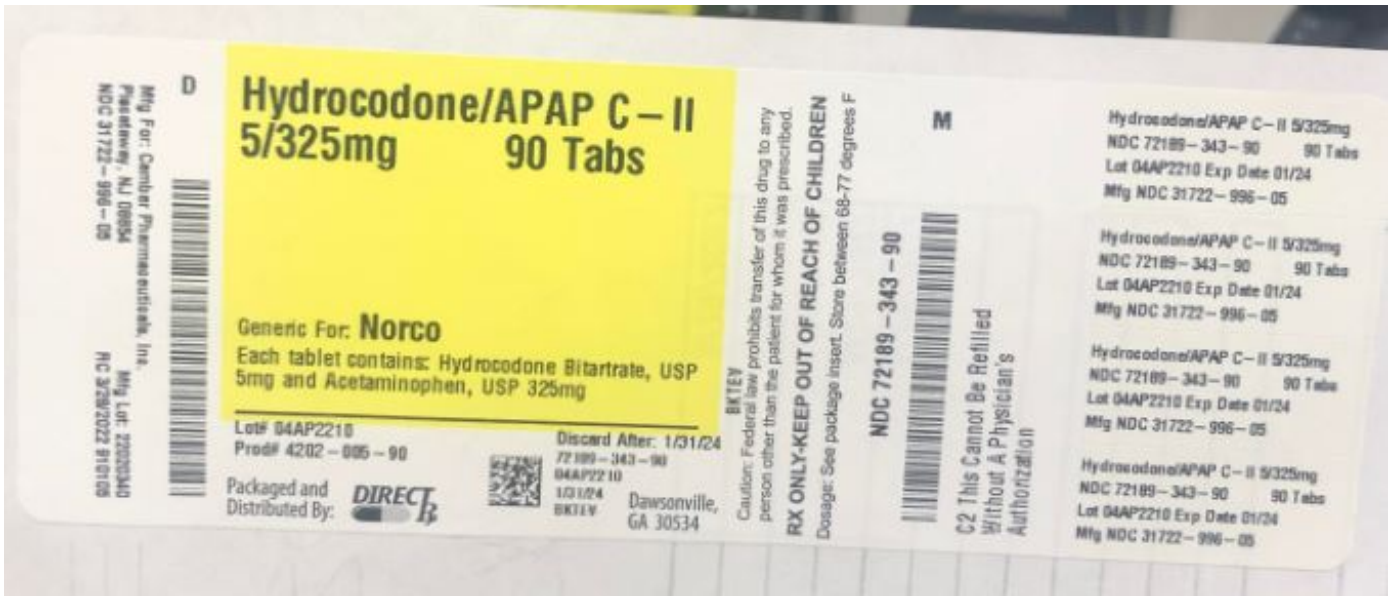
HOW SUPPLIED

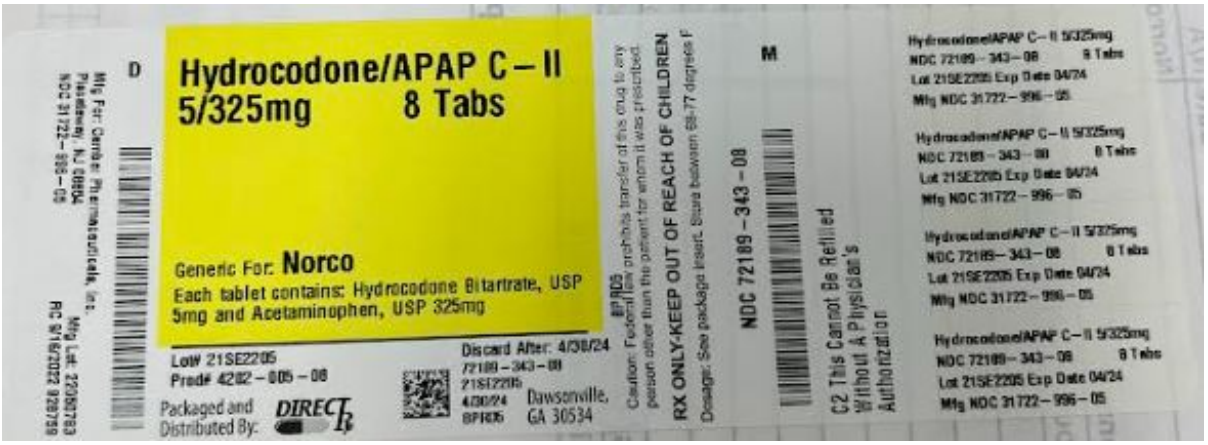
Hydrocodone Bitartrate and Acetaminophen Tablets, USP are supplied as
5 mg/325 mg
containing 5 mg hydrocodone bitartrate and 325 mg acetaminophen. Off white/white capsule shaped tablet debossed ‘T 257’ on one side and plain on other side with bisect line.
NDC 31722-996-01, Bottles of 100 Tablets
NDC 31722-996-05, Bottles of 500 Tablets
10 mg/325 mg
containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen. Off white/white capsule shaped tablet debossed ‘T 259’ on one side and plain on other side with bisect line.
NDC 31722-997-01, Bottles of 100 Tablets
NDC 31722-997-05, Bottles of 500 Tablets
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure.
Store hydrocodone bitartrate and acetaminophen tablets securely and dispose of properly [see PRECAUTIONS/Information for Patients].
Manufactured by:
Ascent Pharmaceuticals, Inc.
Central Islip, NY 11722
Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854
Revised: 05/21
CLOSE
MEDICATION GUIDE
MEDICATION GUIDE
Hydrocodone Bitartrate (hye" droe koe' done bye tar’ trate) and Acetaminophen (a seet"a min' oh fen) Tablets USP, CII
Hydrocodone Bitartrate and Acetaminophen Tablets are:
A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require an opioid 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 Acetaminophen Tablets:
Get emergency help or call 911 right away if you take too much Hydrocodone Bitartrate and Acetaminophen Tablets (overdose). When you first start taking Hydrocodone Bitartrate and Acetaminophen Tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
Taking Hydrocodone Bitartrate and Acetaminophen Tablets with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
Never give anyone else your Hydrocodone Bitartrate and Acetaminophen Tablets. They

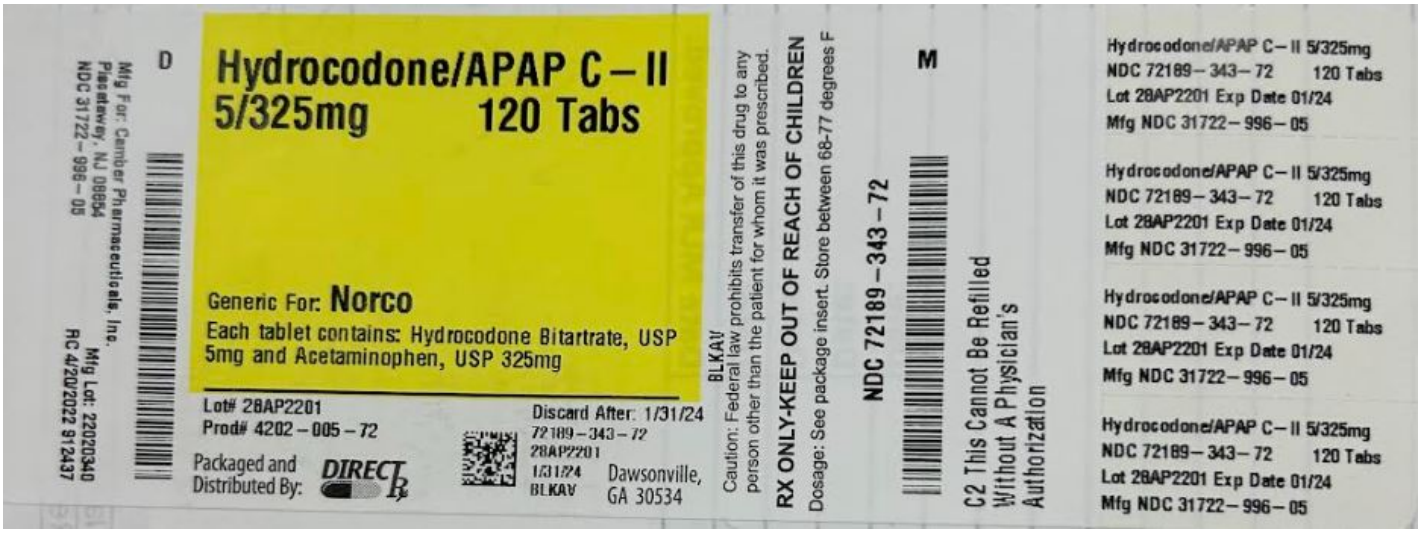
could die from taking it. Selling or giving away Hydrocodone Bitartrate and Acetaminophen Tablets is against the law.
Store Hydrocodone Bitartrate and Acetaminophen Tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
Do not take Hydrocodone Bitartrate and Acetaminophen Tablets if you have:
severe asthma, trouble breathing, or other lung problems.
a bowel blockage or have narrowing of the stomach or intestines.
known hypersensitivity to hydrocodone or acetaminophen, or any ingredient in Hydrocodone Bitartrate and Acetaminophen Tablets
Before taking Hydrocodone Bitartrate and Acetaminophen Tablets, tell your healthcare provider if you have a history of:
head injury, seizures
liver, kidney, thyroid problems
problems urinating
pancreas or gallbladder problems
abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.
Tell your healthcare provider if you are:
pregnant or planning to become pregnant. Prolonged use of Hydrocodone Bitartrate and Acetaminophen Tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
breastfeeding. Hydrocodone bitartrate and acetaminophen passes into breast milk and may harm your baby.
living in a household where there are small children or someone who has abused street or prescription drugs.
taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking Hydrocodone Bitartrate and Acetaminophen Tablets with certain other medicines can cause serious side effects that could lead to death.
When taking Hydrocodone Bitartrate and Acetaminophen Tablets:
Do not change your dose. Take Hydrocodone Bitartrate and Acetaminophen Tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
Take your prescribed dose every 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 Acetaminophen Tablets regularly, do not stop taking Hydrocodone Bitartrate and Acetaminophen Tablets without talking to your healthcare provider.
Dispose of expired, unwanted, or unused Hydrocodone Bitartrate and Acetaminophen 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 Acetaminophen Tablets DO NOT:
Drive or operate heavy machinery, until you know how Hydrocodone Bitartrate and Acetaminophen Tablets affect you. Hydrocodone Bitartrate and Acetaminophen Tablets can make you sleepy, dizzy, or lightheaded.
Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with Hydrocodone Bitartrate and

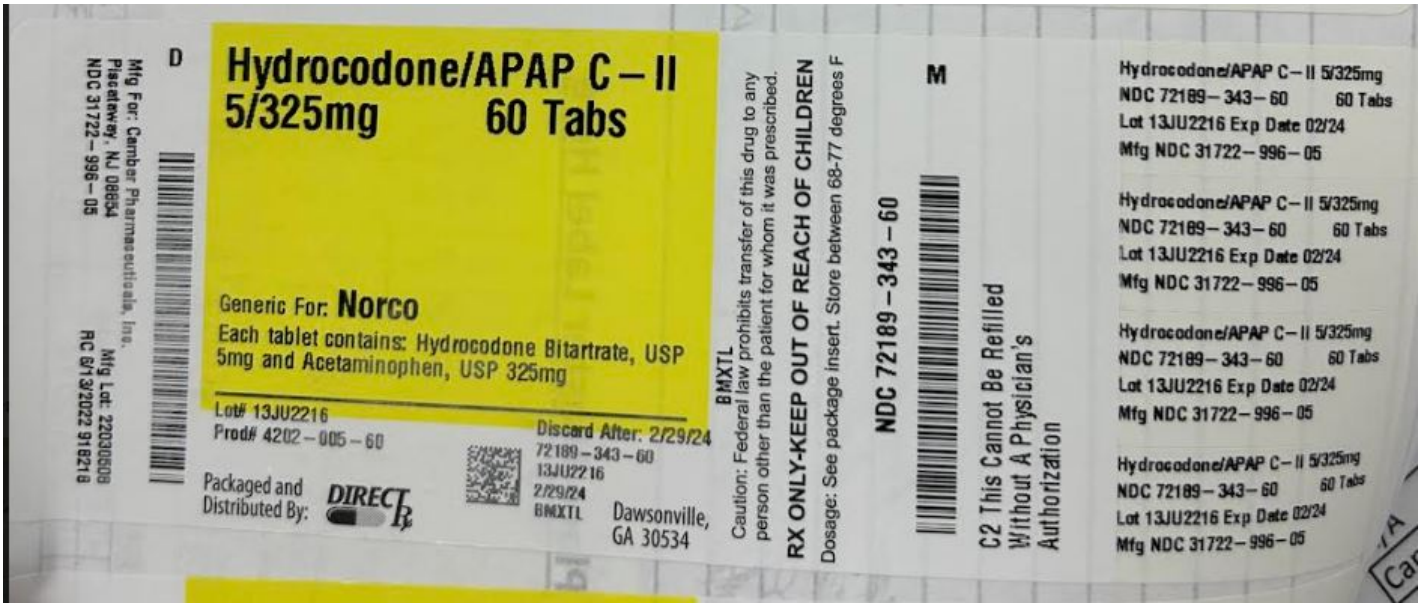
Acetaminophen Tablets may cause you to overdose and die.
The possible side effects of Hydrocodone Bitartrate and Acetaminophen Tablets: constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.
Get emergency medical help or call 911 right away if you have:
trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
These are not all the possible side effects of Hydrocodone Bitartrate and Acetaminophen Tablets. Call your doctor for medical advice about side effects. You may report side effects to Camber Pharmaceuticals Inc., at 1-866-495-8330 or to FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov
Manufactured by:
Ascent Pharmaceuticals, Inc.
Central Islip, NY 11722
Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854
This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: 05/21


Hydrocodone/APAP C – II 5/325mg 30 Tabs
Generic For: Norco
Each tablet contains: Hydrocodone Bitartrate, USP 5mg and Acetaminophen, USP 325mg
Lot# 29MA2218
Prod# 4202 – 005 – 30
Discard After: 1/31/24
72189 – 343 – 30
29MA2218
1/31/24
BKM18
Packaged and Distributed By: DIRECT Rx
Dawsonville, GA 30534
BKMTB
D
Mfg For: Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854
NDC 31722 – 996 – 05
Mfg Lot: 22020340
RC 3/28/2022 910108
Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.
RX ONLY-KEEP OUT OF REACH OF CHILDREN
Dosage: See package insert. Store between 68-77 degrees F
NDC 72189 – 343 – 30
M
C2 This Cannot be Refilled Without A Physician's Authorization
Hydrocodone/APAP C – II 5/325mg
NDC 72189 – 343 – 30 30 Tabs
Lot 29MA2218 Exp Date 01/24
Mfg NDC 31722 – 996 – 05


Hydrocodone/APAP C – II 5/325mg 90 Tabs
Generic For: Norco
Each tablet contains: Hydrocodone Bitartrate, USP 5mg and Acetaminophen, USP 325mg
Lot# 04AP2210
Prod# 4202 – 005 – 90
Discard After: 1/31/24
72189 – 343 – 90
04AP2210
1/31/24
BKTEY
Packaged and Distributed By: DIRECT Rx
Dawsonville, GA 30534
D
Mfg For: Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854
NDC 31722 – 996 – 05
Mfg Lot: 22020340
RC 3/28/2022 910108
Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.
RX ONLY-KEEP OUT OF REACH OF CHILDREN
Dosage: See package insert. Store between 68-77 degrees F
NDC 72189 – 343 – 90
M
C2 This Cannot Be Refilled Without A Physician's Authorization
Hydrocodone/APAP C – II 5/325mg
NDC 72189 – 343 – 90 90 Tabs
Lot 04AP2210 Exp Date 01/24
Mfg NDC 31722 – 996 – 05







HYDROCODONE BITARTRATE AND ACETAMINOPHEN

hydrocodone bitartrate and acetaminophen tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72189-343(NDC:31722-996)

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
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D)	ACETAMINOPHEN	325 mg

Inactive Ingredients

Ingredient Name	Strength
STEARIC ACID (UNII: 4ELV7Z65AP)	
STARCH, CORN (UNII: O8232NY3SJ)	
CROSPOVIDONE (UNII: 2S7830E561)	
POVIDONE (UNII: FZ989GH94E)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	white	**Score**	2 pieces
Shape	OVAL (OVAL (capsule))	**Size**	13mm
Flavor		**Imprint Code**	T257
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-343-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2022	
2	NDC:72189-343-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2022	
3	NDC:72189-343-72	120 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2022	
4	NDC:72189-343-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2022	
5	NDC:72189-343-08	8 in 1 BOTTLE; Type 0: Not a Combination Product	09/22/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211487	03/30/2022	

Labeler - Direct Rx (079254320)

Registrant - Direct Rx (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
Direct Rx		079254320	relabel(72189-343)

Revised: 7/2023

Direct Rx