HYDROCODONE BITARTRATE AND ACETAMINOPHEN- hydrocodone bitartrate and acetaminophen tablet
AvKARE, Inc.

Hydrocodone Bitartrate and Acetaminophen Tablets, USP CII

7.5 mg/325 mg and 10 mg/325 mg

Rx only

BOXED WARNING SECTION

BOXED WARNING

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATIC ENZYME WARNING, DRUG INTERACTION, HEPATOTOXICITY AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse
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 or conditions [see WARNINGS].

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 even one dose 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 bitartrate and acetaminophen tablets 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 bitartrate and acetaminophen tablets plasma concentrations. Monitor patients receiving hydrocodone bitartrate and acetaminophen tablets and any CYP3A4 inhibitor or inducer [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

Drug Interactions

CYP3A4
Inhibitor
The concomitant use of hydrocodone bitartrate and acetaminophen tablets and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g., ritonavir), can increase the plasma concentration of hydrocodone bitartrate and acetaminophen tablets resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of hydrocodone bitartrate and

acetaminophen tablets and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of hydrocodone bitartrate and acetaminophen tablets is achieved [see WARNINGS].

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

Drug/Drug Interactions with Hydrocodone
Opioid analgesics may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increase in the degree of respiratory depression [see WARNINGS].

Drug/Drug Interactions with Acetaminophen
Alcohol, ethyl: Hepatotoxicity has occurred in chronic alcoholics following various dose levels (moderate to excessive) of acetaminophen [see WARNINGS].

Hepatotoxicity
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product.

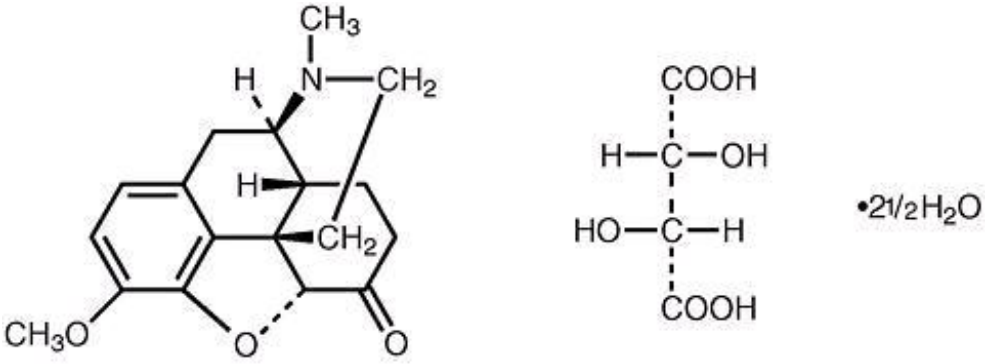
WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see WARNINGS, PRECAUTIONS; 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.

DESCRIPTION

Hydrocodone bitartrate and acetaminophen tablets, USP are supplied in tablet form for oral administration.

WARNING: May be habit-forming (see **PRECAUTIONS, Information For Patients**, and **DRUG ABUSE AND DEPENDENCE**).

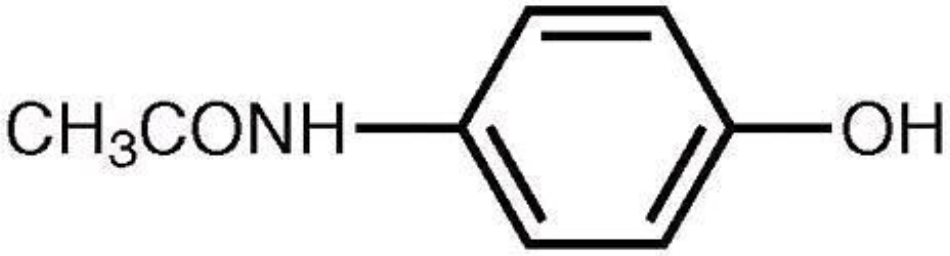
Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

MW = 494.49

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:



$C_8H_9NO_2$

MW = 151.16

Each Hydrocodone bitartrate and acetaminophen tablet, USP contains:

Hydrocodone bitartrate, USP ..... 7.5 mg

Acetaminophen, USP ..... 325 mg

Each hydrocodone bitartrate and acetaminophen tablet, USP 10 mg/325 mg contains:

Hydrocodone bitartrate, USP ..... 10 mg

Acetaminophen, USP ..... 325 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and stearic acid.

Meets USP Dissolution Test 1.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

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.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. 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. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the management of moderate to moderately severe 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 for use in patients for whom alternative treatment options [e.g., non-opioid analgesics].

• Have not been tolerated, or are not expected to be tolerated,

• Have not provided adequate analgesia, or are not expected to provide adequate analgesia

CONTRAINDICATIONS

Hydrocodone bitartrate and acetaminophen tablets is contraindicated in patients with:

• Significant respiratory depression [see WARNINGS].

• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see WARNINGS].

• Hydrocodone bitartrate and acetaminophen tablets should not be administered to patients with known hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

• Hydrocodone is contraindicated in any situation where opioids are contraindicated including patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment) and patients with acute or severe bronchial asthma or hypercarbia. Hydrocodone is contraindicated in the setting of suspected or known paralytic ileus.

WARNINGS

Addiction, Abuse, and Misuse

Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone bitartrate, a Schedule II controlled substance. As an opioid, hydrocodone and acetaminophen tablets exposes users to the risks of addiction, abuse, and misuse [see DRUG ABUSE AND DEPENDENCE].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets, and monitor all patients receiving hydrocodone bitartrate and acetaminophen tablets for the development of these behaviors or 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 acetaminophen tablets, but use in such patients necessitates intensive counseling about the risks and proper use of hydrocodone bitartrate and acetaminophen tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

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

Life-Threatening Respiratory Depression

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

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of hydrocodone bitartrate and acetaminophen tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of hydrocodone bitartrate and acetaminophen tablets.

To reduce the risk of respiratory depression, proper dosing and titration of hydrocodone bitartrate and acetaminophen tablets are essential [see DOSAGE AND ADMINISTRATION]. Overestimating the hydrocodone bitartrate and acetaminophen tablets dosage when converting patients from another opioid

product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of hydrocodone bitartrate and acetaminophen tablets, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone bitartrate. In case of respiratory depression, a reversal agent such as naloxone hydrochloride may be utilized [see OVERDOSAGE].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of hydrocodone bitartrate and acetaminophen tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. 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 PRECAUTIONS; Information for Patients, Pregnancy].

Drug/Drug Interactions with Hydrocodone

Opioid analgesics may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increase in the degree of respiratory depression.

Patients receiving CNS depressants such as other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, centrally-acting anti-emetics, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. The concurrent use of anticholinergics with opioids may produce paralytic ileus.

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, naltrexone, and butorphanol) should be administered with caution to a patient who has received or is receiving a pure opioid agonist such as hydrocodone. These agonist/antagonist analgesics may reduce the analgesic effect of hydrocodone or may precipitate withdrawal symptoms.

Drug/Drug Interactions with Acetaminophen

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

Anticholinergics: The onset of acetaminophen effect may be delayed or decreased slightly, but the ultimate pharmacological effect is not significantly affected by anticholinergics.

Oral Contraceptives: Increase in glucuronidation resulting in increased plasma clearance and a decreased half-life of acetaminophen.

Charcoal (activated): Reduces acetaminophen absorption when administered as soon as possible after overdose.

Beta Blockers (Propanolol): Propranolol appears to inhibit the enzyme systems responsible for the glucuronidation and oxidation of acetaminophen. Therefore, the pharmacologic effects of acetaminophen may be increased.

Loop diuretics: The effects of the loop diuretic may be decreased because acetaminophen may decrease renal prostaglandin excretion and decrease plasma renin activity.

Lamotrigine: Serum lamotrigine concentrations may be reduced, producing a decrease in therapeutic effects.

Probenecid: Probenecid may increase the therapeutic effectiveness of acetaminophen slightly.

Zidovudine: The pharmacologic effects of zidovudine may be decreased because of enhanced nonhepatic or renal clearance of zidovudine.

Drug/Laboratory Test Interactions

Depending on the sensitivity/specificity and the test methodology, the individual components of hydrocodone bitartrate and acetaminophen 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.

Acetaminophen may interfere with home blood glucose measurement systems; decreases of > 20% in mean glucose values may be noted. This effect appears to be drug, concentration and system dependent.

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

Concomitant use of hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see WARNINGS], particularly when an inhibitor is added after a stable dose of hydrocodone bitartrate and acetaminophen tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in hydrocodone bitartrate and acetaminophen tablets treated patients may increase hydrocodone bitartrate and acetaminophen tablets plasma concentrations and prolong opioid adverse reactions. When using hydrocodone bitartrate and acetaminophen tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in hydrocodone bitartrate and acetaminophen tablets treated patients, monitor patients closely at frequent intervals and consider dosage reduction of hydrocodone bitartrate and acetaminophen tablets until stable drug effects are achieved (Note to applicant: If there is a specific dosage adjustment, include the dosage adjustment in the D&A section and include the cross-reference in this section) [see PRECAUTIONS; Drug Interactions, DOSAGE AND ADMINISTRATION].

Concomitant use of hydrocodone bitartrate and acetaminophen tablets with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease hydrocodone bitartrate and acetaminophen tablets plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone and acetaminophen tablets. When using hydrocodone bitartrate and acetaminophen 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 [see PRECAUTIONS; Drug Interactions, DOSAGE AND ADMINISTRATION].

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 acetaminophen tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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

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

Advise both patients and caregivers about the risks of respiratory depression and sedation when hydrocodone bitartrate and acetaminophen 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 and PRECAUTIONS; Information for Patients].

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

The use of hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets treated patients with significant chronic obstructive pulmonary disease or cor-pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of hydrocodone bitartrate and acetaminophen tablets [see WARNINGS].

Elderly, Cachetic, 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].

Monitor such patients closely, particularly when initiating and titrating hydrocodone bitartrate and acetaminophen tablets is given concomitantly with other drugs that depress respiration [see WARNINGS]. Alternatively, consider the use of non-opioid analgesics in these patients.

Adrenal Insufficiency

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

Pregnancy

Teratogenic Effects

Pregnancy Category C:
Animal reproductive studies have not been conducted with hydrocodone and acetaminophen. It is also not known whether hydrocodone and acetaminophen can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Hydrocodone bitartrate and acetaminophen tablets should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Opioids can cross the placental barrier and have the potential to cause neonatal respiratory depression. Opioid use during pregnancy may result in a physically drug-dependent fetus. After birth, the neonate may suffer severe withdrawal symptoms.

Labor and Delivery

Hydrocodone and acetaminophen tablets are not recommended for use in women during and immediately prior to labor and delivery due to its potential effects on respiratory function in the newborn.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Special precaution should be given when determining the dosing amount and frequency of hydrocodone bitartrate and acetaminophen tablets for geriatric patients, since clearance of hydrocodone may be slightly reduced in this patient population when compared to younger patients.

Hepatic Impairment

In a pharmacokinetic study of hydrocodone in patients with end-stage liver disease, hydrocodone plasma clearance decreased and the elimination half-life increased. Care should be exercised when hydrocodone is used in patients with hepatic impairment.

Renal Impairment

In a study of patients with end stage renal impairment, mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance. Hydrocodone should be used with caution in patients with renal impairment.

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing

product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen per day, even if they feel well.

Serious skin reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the sign of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hypersensitivity/ anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs include swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritis, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue Hydrocodone Bitartrate and Acetaminophen Tablets, USP immediately and seek medical care if they experience these symptoms. Do not prescribe Hydrocodone Bitartrate and Acetaminophen Tablets, USP for patients with acetaminophen allergy.

Respiratory Depression

At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions

The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Misuse, Abuse, and Diversion of Opioids

Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, an opioid agonist, and is a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by abusers and people with addiction disorders, and are subject to diversion.

Hydrocodone bitartrate and acetaminophen tablets can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Hydrocodone bitartrate and acetaminophen tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion (see **DRUG ABUSE AND DEPENDENCE**).

PRECAUTIONS

General

Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients/Caregivers

- •Do not take Hydrocodone Bitartrate and Acetaminophen Tablets, USP if you are allergic to any of its ingredients.
- •If you develop signs of allergy such as a rash or difficulty breathing, stop taking Hydrocodone Bitartrate and Acetaminophen Tablets, USP and contact your healthcare provider immediately.
- •Do not take more than 4000 milligrams of acetaminophen per day. Call your doctor if you took more than the recommended dose.

Hydrocodone, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions

Patients receiving other narcotic analgesics, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see ADVERSE REACTIONS].

Pregnancy

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Neonatal Opioid Withdrawal Syndrome
Inform patients that 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 [see WARNINGS, PRECAUTIONS; Pregnancy].

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that hydrocodone bitartrate and acetaminophen tablets can cause fetal harm and to inform the prescriber of a known or suspected pregnancy [see PRECAUTIONS; Pregnancy].

Fetal/Neonatal Adverse Reactions:
Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

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

Labor and Delivery

As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Hydrocodone bitartrate and acetaminophen tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including hydrocodone bitartrate and acetaminophen 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.

Nursing Mothers

Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

maternal condition. Infants exposed to hydrocodone bitartrate and acetaminophen tablets through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of hydrocodone bitartrate and acetaminophen did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, 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. Hydrocodone and the major metabolites of acetaminophen are known to be substantially excreted by the kidney. Thus the risk of toxic reactions may be greater in patients with impaired renal function due to the accumulation of the parent compound and/or metabolites in the plasma. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hydrocodone may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of hydrocodone bitartrate and acetaminophen tablets and observed closely.

Elderly patients (aged 65 years or older) may have increased sensitivity to hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets slowly in geriatric patients [see WARNINGS].

Addiction, Abuse, and Misuse

Inform patients that the use of hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets with others and to take steps to protect hydrocodone bitartrate and acetaminophen 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 acetaminophen 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.

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 acetaminophen tablets securely.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if hydrocodone bitartrate and acetaminophen tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see WARNINGS and PRECAUTIONS; Drug Interactions].

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

Adrenal Insufficiency
Inform patients that hydrocodone bitartrate and acetaminophen tablets 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].

Lactation
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see PRECAUTIONS; Nursing Mothers].

Disposal of unused hydrocodone bitartrate and acetaminophen tablets
Advise patient to destroy unused hydrocodone bitartrate and acetaminophen tablets by flushing down the toilet.

Drug Interactions

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

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone bitartrate and acetaminophen tablets 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 bitartrate and acetaminophen tablets.

If concomitant use is necessary, consider dosage reduction of hydrocodone bitartrate and acetaminophen tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the hydrocodone bitartrate and acetaminophen tablets dosage until stable drug effects are achieved [see DOSAGE AND ADMINISTRATION]. Monitor for signs of opioid withdrawal.

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

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone bitartrate and acetaminophen tablets plasma concentration will increase [see CLINICAL PHARMACOLOGY], which

could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

If concomitant use is necessary, consider increasing the hydrocodone bitartrate and acetaminophen tablets dosage until stable drug effects are achieved [see DOSAGE AND ADMINISTRATION]. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider hydrocodone bitartrate and acetaminophen tablets dosage reduction and monitor for signs of respiratory depression.

Benzodiazepines and other Central Nervous System (CNS) Depressants
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increases the risk of respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see WARNINGS].

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

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

ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

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

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers (see **OVERDOSAGE**).

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

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis. Potential effects of high dosage are listed in the

OVERDOSAGE section.

Postmarketing Experience

- serotonin syndrome
- adrenal insufficiency

Androgen deficiency
Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms of hypogonadism, such as impotence, erectile dysfunction, or amenorrhea. 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. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

To report SUSPECTED ADVERSE REACTIONS, contact AvKARE, Inc. at 1-855-361-3993 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

DRUG ABUSE AND DEPENDENCE

Misuse, Abuse, and Diversion of Opioids

Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, an opioid agonist, and is a Schedule II controlled substance. Hydrocodone bitartrate and acetaminophen tablets, and other opioids, used in analgesia can be abused and are subject to criminal diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease utilizing a multidisciplinary approach, but relapse is common.

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

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physical dependence usually assumes clinically significant dimensions only after several weeks of continued opioid use, although a mild degree of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients. Physicians should be aware that abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Hydrocodone bitartrate and acetaminophen tablets, like other opioids, may be diverted for non-medical use. Record-keeping of prescribing information, including quantity, frequency, and renewal requests 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.

Controlled Substance

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

Abuse
Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone bitartrate, a substance with a high potential for abuse similar to other opioids including hydrocodone bitartrate and acetaminophen tablets can be abused and is subject to misuse, addiction, and criminal diversion [see WARNINGS].

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

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

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

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.

Risks Specific to Abuse of Hydrocodone Bitartrate and Acetaminophen Tablets
As an opioid, hydrocodone bitartrate and acetaminophen tablets exposes users to the risks of addiction, abuse, and misuse [see DRUG ABUSE AND DEPENDENCE].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed hydrocodone bitartrate and acetaminophen 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 acetaminophen tablets, and monitor all patients receiving hydrocodone bitartrate and acetaminophen tablets for the development of these behaviors or 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 acetaminophen tablets, but use in such patients necessitates intensive counseling about the risks and proper use of hydrocodone bitartrate and acetaminophen tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

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

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

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

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

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

OVERDOSAGE

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

Signs and Symptoms

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. 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.

Clinical Presentation
Acute overdose 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.

Treatment

A single or multiple drug overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be

employed as indicated. Assisted or controlled ventilation should also be considered.

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

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

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

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

Hydrocodone

For hydrocodone overdose, primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance, and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

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.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient.

However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

Important Dosage and Administration Instructions
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].

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

Patients should be advised not to adjust the medication dose themselves. Instead, they must consult with their prescribing physician.

Patients should be advised that hydrocodone bitartrate and acetaminophen tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).

Initial Dosage

Use of Hydrocodone Bitartrate and Acetaminophen Tablets as the First Opioid Analgesic
Initiate treatment with hydrocodone bitartrate and acetaminophen tablets in a dosing range of one or two tablets every 4 to 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams.

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.

Dosage Modifications in Patients with Concomitant Use or Discontinuation of Cytochrome P450 3 A4 Inhibitors and Inducers:
When using hydrocodone bitartrate and acetaminophen 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 [see PRECAUTIONS; Drug Interactions].

Dosage Modifications with Concomitant Use with Central Nervous System Depressants:
If the decision to begin hydrocodone bitartrate and acetaminophen tablets is made, start with a lower dosage of hydrocodone bitartrate and acetaminophen tablets [see PRECAUTIONS; Drug Interactions].

Dosage Modifications in Geriatric Patients:
Special precaution should be given when determining the dosing amount and frequency of hydrocodone bitartrate and acetaminophen tablets for geriatric patients [see PRECAUTIONS; Geriatric Patients].

Dosage Modifications in Pediatric Patients:
Safety and effectiveness in pediatric patients have not been established [see PRECAUTIONS; Pediatric Patients].

Dosage Modification in Patients with Chronic Pulmonary Disease are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of hydrocodone bitartrate and acetaminophen tablets [see WARNINGS].

Dosage Modifications in Patients with Renal Impairment:
Hydrocodone should be used with caution in patients with renal impairment.

Dosage Modifications in Patients with Hepatic Impairment:
Care should be exercised when hydrocodone is used in patients with hepatic impairment.

Dosage Modifications in Elderly, Cachetic, or Debilitated Patients:
Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients. Monitor such patients closely, particularly when initiating and titrating hydrocodone bitartrate and acetaminophen tablets and when hydrocodone bitartrate and acetaminophen tablets is given concomitantly with other drugs.

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.

Discontinuation of Hydrocodone Bitartrate and Acetaminophen Tablets
When a patient who has been taking hydrocodone bitartrate and acetaminophen tablets regularly and may be physically dependent no longer requires therapy with hydrocodone bitartrate and acetaminophen tablets, use a gradual downward titration of the dosage to prevent signs and symptoms of withdrawal. Do not stop hydrocodone bitartrate and acetaminophen tablets abruptly [see WARNINGS, DRUG ABUSE AND DEPENDENCE].

HOW SUPPLIED

Hydrocodone bitartrate and acetaminophen tablets, USP **7.5 mg/325** mg are supplied as white to off-white, scored, oblong biconvex tablets, debossed “IP 115” on obverse and bisected on the reverse. Each tablet contains 7.5 mg hydrocodone bitartrate and 325 mg acetaminophen.

They are available as follows:

Bottles of 100: NDC 42291-333-01

Hydrocodone bitartrate and acetaminophen tablets, USP **10 mg / 325 mg** are supplied as white to off-white, scored, oblong biconvex tablets, debossed “IP 110” on obverse and bisected on the reverse. Each tablet contains 10 mg hydrocodone bitartrate and 325 mg acetaminophen.

They are available as follows:

Bottles of 100: NDC 42291-334-01

Storage: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container with a child-resistant closure.

A Schedule CII Narcotic.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 09-2016-00 AV Rev. 10/16

SPL MEDGUIDE SECTION

Medication Guide

Hydrocodone Bitartrate and Acetaminophen
(hye-droe-KOE-dohne bye-TAR-trate/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 moderate to moderately severe pain, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
• An opioid pain medicine 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 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.
• 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. Store hydrocodone bitartrate and acetaminophen tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away hydrocodone bitartrate and acetaminophen tablets is against the law.

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.

Before taking hydrocodone bitartrate and acetaminophen tablets, tell your healthcare provider if you have a history of:
• head injury, seizures
• problems urinating
• liver, kidney, thyroid problems
• pancreas or gallbladder problems
• abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:
• **pregnant or planning to become pregnant.** Prolonged use of 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 and acetaminophen passes into breast milk and may harm your baby.
• 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.
• Take your prescribed dose every 6 hours at the same time every day. 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.
• After you stop taking hydrocodone bitartrate and acetaminophen tablets dispose of unused drug.

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 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 FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov

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

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg Rev. 09-2016-00 AV Rev. 10/16

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

AvKARE

NDC 42291- **333**-01

CII

Hydrocodone Bitartrate and Acetaminophen Tablets, USP

7.5 mg/ 325 mg

Dispense the accompanying Medication Guide to each patient.

MULTIPLE STRENGTHS: DO NOT DISPENSE UNLESS STRENGTH IS STATED

100 Tablets **Rx only**

Each tablet contains:

Hydrocodone Bitartrate, USP.....7.5 mg

WARNING: May be habit forming.
Acetaminophen, USP.....325 mg

USUAL DOSAGE: See package insert for complete dosage recommendations.

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

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.
Protect from light.

STORAGE: Store at 20 º to 25 ºC (68 º to 77 ºF); excursions permitted to 15 º to 30 ºC (59 º to 86 ºF) [see USP Controlled Room Temperature].

DEA ORDER FORM REQUIRED.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 09-2016-01 AV 10/16

N3 42291 33301 7

AvKARE

NDC 42291- **334**-01

CII

Hydrocodone Bitartrate and Acetaminophen Tablets, USP

10 mg/ 325 mg

Dispense the accompanying Medication Guide to each patient.

MULTIPLE STRENGTHS: DO NOT DISPENSE UNLESS STRENGTH IS STATED

100 Tablets **Rx only**

Each tablet contains:
Hydrocodone Bitartrate, USP.....10 mg

WARNING: May be habit forming.
Acetaminophen, USP.....325 mg

USUAL DOSAGE: See package insert for complete dosage recommendations.

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DEA ORDER FORM REQUIRED.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 04-2016-02 AV 10/16

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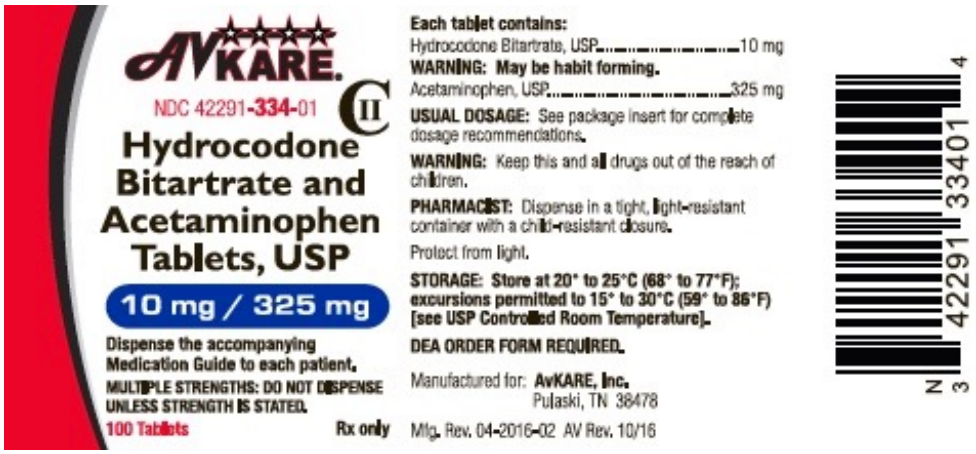

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

hydrocodone bitartrate and acetaminophen tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42291-333
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE -	HYDROCODONE	7.5 mg

UNII:6YKS4Y3WQ7)	BITARTRATE	7.5 mg
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D)	ACETAMINOPHEN	325 mg

Inactive Ingredients	
Ingredient Name	**Strength**
POVIDONE (UNII: FZ989GH94E)	
STARCH, CORN (UNII: O8232NY3SJ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	

Product Characteristics			
Color	white (off-white)	**Score**	2 pieces
Shape	CAPSULE	**Size**	15mm
Flavor		**Imprint Code**	IP;115
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-333-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/06/2016	02/28/2019

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040746	09/06/2016	02/28/2019

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

hydrocodone bitartrate and acetaminophen tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42291-334
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	10 mg
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D)	ACETAMINOPHEN	325 mg

Inactive Ingredients	
Ingredient Name	**Strength**
POVIDONE (UNII: FZ989GH94E)	

SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
CROSPOVIDONE (12 MPA.S AT 5%) (UNII: 40UAA97IT9)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	white (off-white)	**Score**	2 pieces
Shape	CAPSULE	**Size**	15mm
Flavor		**Imprint Code**	IP;110
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-334-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/06/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040746	09/06/2016	

Labeler - AvKARE, Inc. (796560394)

Revised: 4/2019 AvKARE, Inc.