

**HYDROCODONE BITARTRATE AND ACETAMINOPHEN- hydrocodone bitartrate and
acetaminophen tablet
Aidarex Pharmaceuticals LLC**

Hydrocodone Bitartrate and Acetaminophen Tablets USP

**Hydrocodone Bitartrate and
Acetaminophen Tablets, USP
CII**

Revised: April 2016

Rx Only

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION and HEPATOTOXICITY

Addiction, Abuse, and Misuse

Hydrocodone bitartrate and acetaminophen tablets exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing 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 concentration. Monitor patients receiving hydrocodone bitartrate and acetaminophen tablets and any CYP3A4 inhibitor or inducer [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

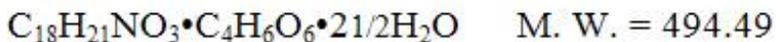
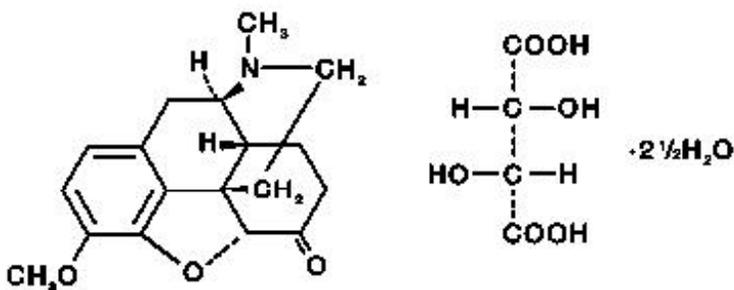
Hepatotoxicity

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 4000 milligrams per day, and often involve more than one acetaminophen containing product.

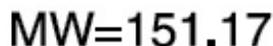
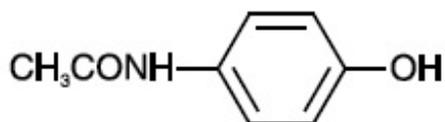
DESCRIPTION

Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

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 4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



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:



Hydrocodone Bitartrate and Acetaminophen Tablets, USP for oral administration are available in a variety of strengths as described in the following table.

<u>Strength</u>	<u>Hydrocodone Bitartrate</u>	<u>Acetaminophen</u>
2.5 mg/325 mg	2.5 mg	325 mg
5 mg/325 mg	5 mg	325 mg
7.5 mg/325 mg	7.5 mg	325 mg
10 mg/325 mg	10 mg	325 mg

In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium and magnesium stearate. 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-ketoreduction 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 are contraindicated in patients with:

- Significant respiratory depression [see **WARNINGS**]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see **WARNINGS**]
- Patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.
- Known hypersensitivity to other opioids who may exhibit cross-sensitivity to hydrocodone.

WARNINGS

Addiction, Abuse, and Misuse

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

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed hydrocodone bitartrate and 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 tablet 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 (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of hydrocodone bitartrate and 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 24-72 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.

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**].

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 signs 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 included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, 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.

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 pre-existing 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.

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 tablet-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 tablet-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of hydrocodone bitartrate and acetaminophen tablets until stable drug effects are achieved [see **PRECAUTIONS; Drug Interactions**].

Concomitant use of hydrocodone bitartrate and acetaminophen tablets with CYP3A4 inducers or discontinuation of a 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 bitartrate 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 occur [see **PRECAUTIONS; Drug Interactions**].

Risks due to Interactions with Central Nervous System Depressants

Hypotension, profound sedation, respiratory depression, coma, and death may result if hydrocodone bitartrate and acetaminophen tablets are used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., benzodiazepines and other sedatives/hypnotics, anxiolytics, and tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids).

When considering the use of hydrocodone bitartrate and acetaminophen tablets in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that can cause CNS depression. If the decision to begin hydrocodone bitartrate and acetaminophen tablets is made, start with a lower dosage of hydrocodone bitartrate and acetaminophen tablets, monitor patients for signs of respiratory depression, sedation, and hypotension, and consider using a lower dose of the concomitant CNS depressant [see **PRECAUTIONS; Drug Interactions**].

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

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see **WARNINGS**].

Monitor such patients closely, particularly when initiating and titrating hydrocodone bitartrate and acetaminophen tablets and when hydrocodone bitartrate and acetaminophen tablets are 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.

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.

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 and to dispose of unused hydrocodone bitartrate and acetaminophen tablets by flushing any unused tablets down the toilet.

Interactions with Alcohol and Other CNS Depressants

Inform patients that potentially serious additive effects may occur if hydrocodone bitartrate and acetaminophen tablets are used with alcohol or other CNS depressants and not to use such drugs unless supervised by a health care provider [see **WARNINGS, 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 lifethreatening 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**].

Pregnancy

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**].

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 patients to flush any unused tablets down the toilet.

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 narcotics, antihistamines, antipsychotics, antianxiety 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.

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**].

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

Central Nervous System Depressants

Due to additive pharmacologic effect, the concomitant use of CNS depressants such as alcohol, benzodiazepines and other sedative hypnotics, anxiolytics, and tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Consider dose reduction of one or both drugs. Monitor patients for signs of respiratory depression, sedation, and hypotension [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.

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

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 or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. 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

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 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

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**].

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory 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, and 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 center (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.

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 used in analgesia. 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.

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

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

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. Abuse of hydrocodone bitartrate and acetaminophen tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of hydrocodone bitartrate and acetaminophen tablets with alcohol and other substances.

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 are abruptly discontinued in a physically dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

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

OVERDOSAGE

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.

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.

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 in 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.

DOSAGE AND ADMINISTRATION

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 24-72 hours of initiating therapy and following dosage increases with hydrocodone bitartrate and acetaminophen tablets and adjust the dosage accordingly [see **WARNINGS**].

Initial Dosage

Initiating Treatment with Hydrocodone Bitartrate and Acetaminophen Tablets

2.5 mg/325 mg 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.
	The usual adult dosage is one tablet every

7.5 mg/325 mg	four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
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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.
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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.

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 are available in the following strengths:

2.5 mg/325 mg 2.5 mg hydrocodone bitartrate and 325 mg acetaminophen, capsule shaped, white tablets, debossed with **2171** on one side:

120 TABLET in a BOTTLE
(53217-192-02)

30 TABLET in a BOTTLE
(53217-192-30)

60 TABLET in a BOTTLE
(53217-192-60)

90 TABLET in a BOTTLE
(53217-192-90)

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

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

Repackaged by

Aidarex Pharmaceuticals, LLC

Corona, CA 92880

Medication Guide

Hydrocodone Bitartrate and Acetaminophen

(hye" droe koe' done bye tar' trate and 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.

- Never give anyone else your hydrocodone bitartrate and acetaminophen tablets. They could die from taking them. 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.
- signs or allergy such as a rash.
- are allergic to any of its ingredients.

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, 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.
- 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 four to six 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, flush any unused tablets down the toilet.

While taking hydrocodone bitartrate and acetaminophen tablets DO NOT:

- Drive or operate heavy machinery, until you know how hydrocodone bitartrate and acetaminophen tablets affects 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 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**

For more information call Actavis at 1-800-272-5525.

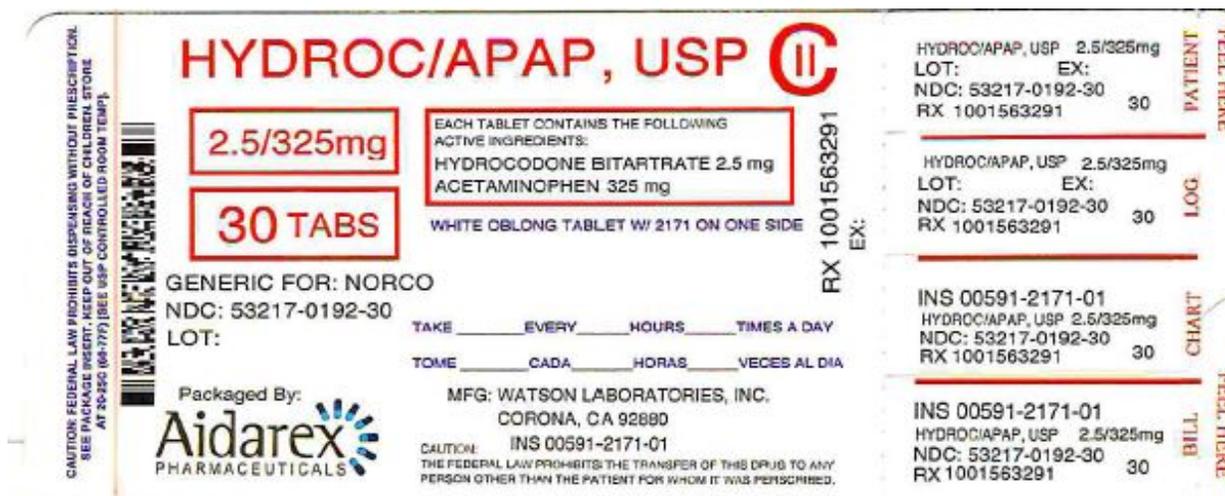
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Warner Chilcott Company, LLC
Manati, Puerto Rico
00674

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

Revised: April 2016

PRINCIPAL DISPLAY PANEL



SPL Image

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

hydrocodone bitartrate and acetaminophen tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:53217-192(NDC:0591-2171)
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
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HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	2.5 mg
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D)	ACETAMINOPHEN	325 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	WHITE	Score	no score
Shape	OVAL (capsule-shaped)	Size	25mm
Flavor		Imprint Code	2171
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:53217-192-02	02 in 1 BOTTLE; Type 0: Not a Combination Product	10/06/2014	
2	NDC:53217-192-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	10/06/2014	
3	NDC:53217-192-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	10/06/2014	
4	NDC:53217-192-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	10/06/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040148	10/06/2014	

Labeler - Aidarex Pharmaceuticals LLC (801503249)

Revised: 3/2017

Aidarex Pharmaceuticals LLC