ACETAMINOPHEN AND CODEINE- acetaminophen and codeine tablet
RedPharm Drug, Inc.

Acetaminophen and Codeine 300/30mg tabs

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF CODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse

Acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets, and monitor all patients regularly for the development of these behaviors and conditions (see WARNINGS).

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products (see WARNINGS). Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program.**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products.**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist.**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of acetaminophen and codeine phosphate tablets. Monitor for respiratory depression, especially during initiation of acetaminophen and codeine phosphate tablets or following a dose increase (see WARNINGS).

Accidental Ingestion

Accidental ingestion of acetaminophen and codeine phosphate tablets, especially by children, can result in a fatal overdose of acetaminophen and codeine phosphate tablets (see WARNINGS).

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy and many of the children had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism (see WARNINGS, PRECAUTIONS; Information for Patients/Caregivers, Nursing Mothers). Acetaminophen and codeine phosphate tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of acetaminophen and codeine phosphate tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of acetaminophen and codeine phosphate 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).

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with acetaminophen and codeine phosphate tablets requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine (see WARNINGS, PRECAUTIONS: DRUG INTERACTIONS).

Hepatotoxicity

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

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, Drug Interactions).

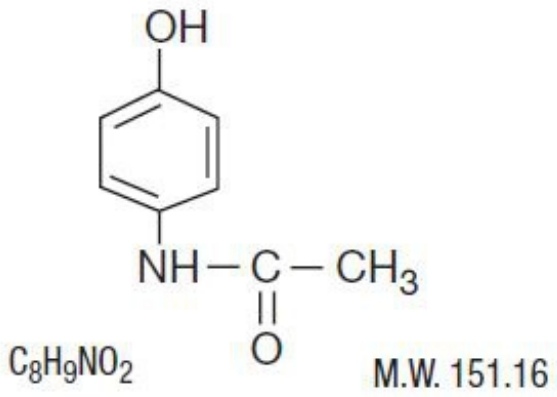
- **Reserve concomitant prescribing of acetaminophen and codeine phosphate tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**

- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

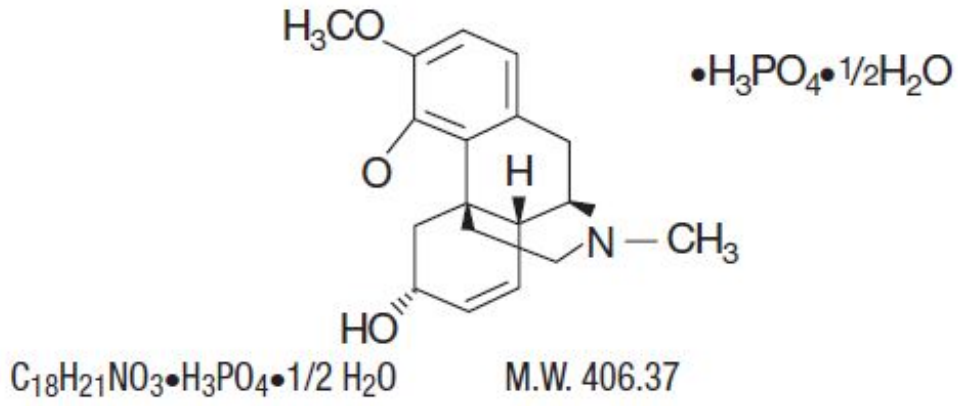
DESCRIPTION

Acetaminophen and codeine phosphate tablets, USP are supplied in tablet form for oral administration.

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:



Codeine phosphate, 7,8-didehydro-4, 5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate, a white crystalline powder, is a narcotic analgesic and antitussive. It has the following structural formula:



Each Acetaminophen and Codeine Phosphate Tablet, USP (300 mg/30 mg) contains:

Acetaminophen ..... 300 mg
Codeine Phosphate ..... 30 mg

In addition, each acetaminophen and codeine phosphate tablet, USP contains the

following inactive ingredients: croscarmellose sodium, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and stearic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action

Codeine is an opioid agonist relatively selective for the mu-opioid receptor, but with a much weaker affinity than morphine. The analgesic properties of codeine have been speculated to come from its conversion to morphine, although the exact mechanism of analgesic action remains unknown.

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

Pharmacodynamics

Effects on the Central Nervous System

Codeine produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Codeine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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

Effects on the Cardiovascular System

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

Effects on the Endocrine System

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

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction,

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

Effects on the Immune System

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

Concentration–Efficacy Relationships

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

Concentration–Adverse Reaction Relationships

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

Pharmacokinetics

The behavior of the individual components is described below.

Codeine

Codeine is rapidly absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen, and kidney. Codeine crosses the blood-brain barrier and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain. Codeine is about 7% to 25% bound to plasma proteins and does not accumulate in body tissues.

About 70% to 80% of the administered dose of codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide (C6G) and via O-demethylation to morphine (about 5 to 10%) and N-demethylation to norcodeine (about 10%) respectively. UDP-glucuronosyltransferase (UGT) 2B7 and 2B4 are the major enzymes mediating glucuronidation of codeine to C6G. Cytochrome P450 2D6 is the major enzyme responsible for conversion of codeine to morphine and P450 3A4 is the major enzyme mediating conversion of codeine to norcodeine. Morphine and norcodeine are further metabolized by conjugation with glucuronic acid. The glucuronide metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Morphine and M6G are known to have analgesic activity in humans. The analgesic activity of C6G in humans is unknown. Norcodeine and M3G are generally not considered to possess analgesic properties.

The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the

kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.

Acetaminophen

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

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

Acetaminophen and codeine phosphate tablets are indicated for the management of mild to moderate pain, where treatment with an opioid is appropriate 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 acetaminophen and codeine phosphate tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics).

- Have not provided adequate analgesia, or are not expected to provide adequate analgesia,
- Have not been tolerated, or are not expected to be tolerated.

CONTRAINDICATIONS

Acetaminophen and codeine phosphate tablets are contraindicated for:

- All children younger than 12 years of age (see **WARNINGS**).
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see **WARNINGS**).

Acetaminophen and codeine phosphate 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**).
- concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (see **WARNINGS**).
- known or suspected gastrointestinal obstruction, including paralytic ileus (see **WARNINGS**).
- hypersensitivity to codeine, acetaminophen, or any of the formulation excipients (e.g., anaphylaxis) (see **WARNINGS**).

WARNINGS

Addiction, Abuse, and Misuse

Acetaminophen and codeine phosphate tablets contain codeine. Codeine in combination with acetaminophen, is a Schedule III controlled substance. As an opioid, acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets, and monitor all patients receiving acetaminophen and codeine phosphate tablets for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as acetaminophen and codeine phosphate tablets, but use in such patients necessitates intensive counseling about the risks and proper use of acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate 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/Caregivers**). 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.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse,

and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

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

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

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 acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets.

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

Accidental ingestion of acetaminophen and codeine phosphate tablets, especially by children, can result in respiratory depression and death due to an overdose of codeine.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using

best practices for opioid taper (see **DOSAGE AND ADMINISTRATION**) .

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- Acetaminophen and codeine phosphate tablets are contraindicated for all children younger than 12 years of age (see **CONTRAINDICATIONS**).
- Acetaminophen and codeine phosphate tablets are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy (see **CONTRAINDICATIONS**).
- Avoid the use of acetaminophen and codeine phosphate tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression (see **WARNINGS**).
- As with adults, when prescribing codeine for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose (see **OVERDOSAGE**).

Nursing Mothers

At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with acetaminophen and codeine phosphate tablets.

CYP2D6 Genetic Variability: Ultra-Rapid Metabolizers

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1% to 10% for Whites (European, North American), 3% to 4% for Blacks (African Americans), 1% to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican).

These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) (see **OVERDOSAGE**). Therefore, individuals who are ultra-rapid metabolizers should not use acetaminophen and codeine phosphate tablets.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of acetaminophen and codeine phosphate tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see **PRECAUTIONS; Information for Patients/Caregivers, Pregnancy**).

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with acetaminophen and codeine phosphate tablets requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

Cytochrome P450 3A4 Interaction

The concomitant use of acetaminophen and codeine phosphate tablets with all cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome P450 2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

The concomitant use of acetaminophen and codeine phosphate tablets with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Follow patients receiving acetaminophen and codeine phosphate tablets and any CYP3A4 inhibitor or inducer for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when acetaminophen and codeine phosphate tablets are used in conjunction with inhibitors and inducers of CYP3A4 (see **WARNINGS; Drug Interactions**).

If concomitant use of a CYP3A4 inhibitor is necessary or if a CYP3A4 inducer is discontinued, consider dosage reduction of acetaminophen and codeine phosphate tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.

If concomitant use of a CYP3A4 inducer is necessary or if a CYP3A4 inhibitor is discontinued, consider increasing the acetaminophen and codeine phosphate tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal (see **PRECAUTIONS; Drug Interactions**).

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use of acetaminophen and codeine phosphate tablets with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in codeine plasma concentrations and a decrease in active metabolite morphine plasma concentration which could result in an analgesic efficacy reduction or symptoms of opioid withdrawal.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

Follow patients receiving acetaminophen and codeine phosphate tablets and any CYP2D6 inhibitor for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when acetaminophen and codeine phosphate tablets are used in conjunction with inhibitors of CYP2D6.

If concomitant use with a CYP2D6 inhibitor is necessary, follow the patient for signs of reduced efficacy or opioid withdrawal and consider increasing the acetaminophen and codeine phosphate tablets dosage. After stopping use of a CYP2D6 inhibitor, consider reducing the acetaminophen and codeine phosphate tablets dosage and follow the patient for signs and symptoms of respiratory depression or sedation (see **PRECAUTIONS; Drug Interactions**).

Hepatotoxicity

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

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of acetaminophen and codeine phosphate tablets with benzodiazepines and/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 acetaminophen and codeine phosphate tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **PRECAUTIONS; Drug Interactions, Information for Patients/Caregivers**).

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

The use of acetaminophen and codeine phosphate 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

Acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets (see **WARNINGS; Life-Threatening Respiratory Depression**).

Elderly, Cachectic, or Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics, including clearance, compared to younger, healthier patients (see **WARNINGS; Respiratory Depression**).

Monitor such patients closely, particularly when initiating and titrating acetaminophen and codeine phosphate tablets and when acetaminophen and codeine phosphate tablets

are given concomitantly with other drugs that depress respiration (see **WARNINGS; Life-Threatening Respiratory Depression**). Alternatively, consider the use of non-opioid analgesics in these patients.

Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, codeine's active metabolite, including respiratory depression, coma, and confusion. Acetaminophen and codeine phosphate tablets should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

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.

Severe Hypotension

Acetaminophen and codeine may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) (see **PRECAUTIONS; Drug Interactions**). Monitor these patients for signs of hypotension after initiating or titrating the dosage of acetaminophen and codeine phosphate tablets. In patients with circulatory shock acetaminophen and codeine phosphate tablets may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of acetaminophen and codeine with circulatory shock.

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.

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

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), acetaminophen and codeine phosphate tablets may reduce respiratory drive, and the resultant CO_2

retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with acetaminophen and codeine phosphate tablets.

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

Hypersensitivity/Anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the 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 acetaminophen and codeine phosphate tablets immediately and seek medical care if they experience these symptoms. Do not prescribe acetaminophen and codeine phosphate tablets for patients with acetaminophen allergy (see **PRECAUTIONS; Information for Patients/Caregivers**).

Risks of Use in Patients with Gastrointestinal Conditions

Acetaminophen and codeine phosphate tablets are contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

The administration of acetaminophen and codeine phosphate tablets or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Acetaminophen and codeine phosphate tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders

The codeine in acetaminophen and codeine phosphate tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during acetaminophen and codeine phosphate tablets therapy.

Withdrawal

Do not abruptly discontinue acetaminophen and codeine phosphate tablets in a patient physically dependent on opioids. When discontinuing acetaminophen and codeine phosphate tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of acetaminophen and codeine phosphate tablets in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain (see **DOSAGE AND ADMINISTRATION**, **DRUG ABUSE AND DEPENDENCE**).

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including acetaminophen and codeine phosphate tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms (see **DRUG INTERACTIONS**).

PRECAUTIONS

Risks of Driving and Operating Machinery

Acetaminophen and codeine phosphate tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of acetaminophen and codeine phosphate tablets and know how they will react to the medication (see **PRECAUTIONS; Information for Patients/Caregivers**).

Information for Patients/Caregivers

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

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store acetaminophen and codeine phosphate tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home (see **WARNINGS, DRUG ABUSE AND DEPENDENCE**). Inform patients that leaving acetaminophen and codeine phosphate tablets unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Inform patients that medicine take-back options are the preferred way to safely dispose of most types of unneeded medicines. If no take back programs or DEA-registered collectors are available, instruct patients to dispose of acetaminophen and codeine phosphate tablets by following these four steps:

- Mix acetaminophen and codeine phosphate tablets (do not crush) with an unpalatable substance such as dirt, cat litter, or used coffee grounds;
- Place the mixture in a container such as a sealed plastic bag;
- Throw the container in the household trash;
- Delete all personal information on the prescription label of the empty bottle

Inform patients that they can visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Addiction, Abuse and Misuse

Inform patients that the use of acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets with others and to take steps to protect acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate 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**).

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue acetaminophen and codeine phosphate tablets without first discussing a tapering plan with the prescriber (see **DOSAGE AND ADMINISTRATION**).

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Advise caregivers that acetaminophen and codeine phosphate tablets are contraindicated in all children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children 12 to 18 years of age receiving acetaminophen and codeine phosphate tablets to monitor for signs of respiratory depression (see **WARNINGS**).

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if acetaminophen and codeine phosphate tablets used with benzodiazepines or other CNS depressants, including alcohol, and not to use these drugs concomitantly unless supervised by a healthcare provider (see **WARNINGS, PRECAUTIONS; Drug Interactions**).

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms and signs of serotonin syndrome and to seek medical attention right away if symptoms develop.

Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications (see **PRECAUTIONS; Drug Interactions**).

MAOI Interaction

Inform patients not to take acetaminophen and codeine phosphate tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking acetaminophen and codeine phosphate tablets (see **WARNINGS; Drug Interactions**).

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms (see **WARNINGS**).

Important Administration Instructions

Instruct patients how to properly take acetaminophen and codeine phosphate tablets (see **DOSAGE AND ADMINISTRATION**).

- Advise patients not to adjust the dose of acetaminophen and codeine phosphate

tablets without consulting a physician or other healthcare professional.

Maximum Daily Dose of Acetaminophen

Inform patients not to take more than 4,000 milligrams of acetaminophen per day. Advise patients to call their healthcare provider if they have taken more than the recommended dose.

Hypotension

Inform patients that acetaminophen and codeine phosphate tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) (see **WARNINGS; Hypotension**).

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in acetaminophen and codeine phosphate tablets. Advise patients how to recognize such a reaction, and if they develop signs of allergy such as a rash or difficulty breathing to stop taking acetaminophen and codeine phosphate tablets and seek medical attention (see **CONTRAINDICATIONS, ADVERSE REACTIONS**).

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of acetaminophen and codeine phosphate tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated (see **WARNINGS; Pregnancy**).

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that acetaminophen and codeine phosphate tablets can cause fetal harm and to inform the prescriber of a known or suspected pregnancy (see **PRECAUTIONS; Pregnancy**).

Lactation

Advise women that breastfeeding is not recommended during treatment with acetaminophen and codeine phosphate tablets (see **PRECAUTIONS; Nursing Mothers)** .

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible.

Driving or Operating Heavy Machinery

Inform patients that acetaminophen and codeine phosphate tablets may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery and to avoid such tasks while taking this product, until they know how they will react to the medication.

Constipation

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

Drug Interactions

CYP2D6 Inhibitors

Codeine is metabolized by CYP2D6 to form morphine. The concomitant use of acetaminophen and codeine phosphate tablets and CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, bupropion, quinidine) can increase the plasma concentration of codeine, but can decrease the plasma concentration of active metabolite morphine, which could result in reduced analgesic efficacy or symptoms of opioid withdrawal, particularly when an inhibitor is added after a stable dose of acetaminophen and codeine phosphate tablets are achieved (see **CLINICAL PHARMACOLOGY**).

After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease but the active metabolite morphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression (see **CLINICAL PHARMACOLOGY**).

If concomitant use with a CYP2D6 inhibitor is necessary, or if a CYP2D6 inhibitor is discontinued after concomitant use, consider dosage adjustment of acetaminophen and codeine phosphate tablets and monitor patients closely at frequent intervals.

If concomitant use with CYP2D6 inhibitors is necessary, follow the patient for reduced efficacy or signs and symptoms of opioid withdrawal and consider increasing the acetaminophen and codeine phosphate tablets as needed.

After stopping use of a CYP2D6 inhibitor, consider reducing the acetaminophen and codeine phosphate tablets and monitor the patient for signs and symptoms of respiratory depression or sedation.

CYP3A4 Inhibitors

The concomitant use of acetaminophen and codeine phosphate tablets and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g., ritonavir), may result in an increase in codeine plasma concentrations, with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of acetaminophen and codeine phosphate tablets is achieved (see **WARNINGS**).

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower codeine levels, greater norcodeine levels, and less metabolism via CYP2D6 with resultant lower morphine levels (see **CLINICAL PHARMACOLOGY**), resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to codeine.

If concomitant use of CYP3A4 inhibitor is necessary, consider dosage reduction of acetaminophen and codeine 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 acetaminophen and

codeine phosphate tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

CYP3A4 Inducers

The concomitant use of acetaminophen and codeine phosphate tablets and CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) can result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels (see **CLINICAL PHARMACOLOGY**), resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence (see **WARNINGS**).

After stopping a CYP3A4 inducer, as the effects of the inducer decline, codeine plasma concentrations may increase, with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels (see **CLINICAL PHARMACOLOGY**), which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

If concomitant use of a CYP3A4 inducer is necessary, follow the patient for reduced efficacy and signs of opioid withdrawal and consider increasing the acetaminophen and codeine phosphate tablets dosage as needed.

If a CYP3A4 inducer is discontinued, consider acetaminophen and codeine phosphate tablets dosage reduction and monitor for signs of respiratory depression and sedation at frequent intervals.

Benzodiazepines and Other Central Nervous System (CNS) Depressants

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

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

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 affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), 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 follow the patient, particularly during treatment initiation and dose adjustment. Discontinue acetaminophen and codeine phosphate tablets if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors (MAOIs)

The concomitant use of opioids and MAOIs, such as phenelzine, tranylcypromine, linezolid, may manifest as serotonin syndrome or opioid toxicity.

Advise patients taking acetaminophen and codeine phosphate tablets not to use MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses of other opioids (such as oxycodone, hydrocodone, oxymorphone or buprenorphine) to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

The concomitant use of opioids with other opioid analgesics, such as butorphanol, nalbuphine, pentazocine, may reduce the analgesic effect of acetaminophen and codeine phosphate tablets and/or precipitate withdrawal symptoms.

Advise patient to avoid concomitant use of these drugs.

Muscle Relaxants

Acetaminophen and codeine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

If concomitant use is warranted, monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of acetaminophen and codeine phosphate tablets and/or the muscle relaxant as necessary.

Diuretics

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

If concomitant use is warranted, monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs

The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

If concomitant use is warranted, monitor patients for signs of urinary retention or reduced gastric motility when acetaminophen and codeine phosphate tablets are used concomitantly with anticholinergic drugs.

Drug/Laboratory Test Interactions

Codeine may increase serum amylase levels.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies to evaluate the carcinogenic potential of the combination of codeine and acetaminophen have not been conducted.

Two-year carcinogenicity studies have been conducted in F344/N rats and B6C3F1 mice. There was no evidence of carcinogenicity in male and female rats, respectively, at dietary

doses up to 70 and 80 mg/kg/day of codeine sulfate (approximately 2 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m ^{2} basis) for two years. Similarly there was no evidence of carcinogenicity activity in male and female mice at dietary doses up to 400 mg/kg/day of codeine sulfate (approximately 5 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m ^{2} basis) for two years.

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6,000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 0.7 times or mice at up to 1.2 to 1.4 times the MHDD, based on a body surface area comparison.

Mutagenesis

Codeine sulfate was not mutagenic in the *in vitro* bacterial reverse mutation assay or clastogenic in the *in vitro* Chinese hamster ovary cell chromosome aberration assay.

In the published literature, acetaminophen has been reported to be clastogenic when administered at 1,500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of Fertility

No nonclinical fertility studies have been conducted with codeine or the combination of codeine and acetaminophen.

In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison.

Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.78 times the MHDD (based on a body surface comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

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

Codeine

A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg subcutaneous dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no adequate and well-controlled studies in pregnant women. Acetaminophen and codeine phosphate tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

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. Acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets, and 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.

Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see **OVERDOSAGE**). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

Codeine and its active metabolite, morphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression, and death in infants exposed to codeine via breast milk. Women who are ultra-rapid metabolizers of codeine achieve higher than expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous in their breastfed infants. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent.

There is no information on the effects of codeine on milk production. Because of the potential for serious adverse reactions, including excess sedation, respiratory depression, and death in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with acetaminophen and codeine phosphate tablets (see **WARNINGS**).

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

Clinical Considerations

If infants are exposed to acetaminophen and codeine phosphate tablets through breast milk, they 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 breastfeeding is stopped.

Pediatric Use

The safety and effectiveness of acetaminophen and codeine phosphate tablets in pediatric patients below the age of 18 have not been established.

Life-threatening respiratory depression and death have occurred in children who received codeine (see **WARNINGS**). In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine. Because of the risk of life-threatening respiratory depression and death:

- Acetaminophen and codeine phosphate tablets are contraindicated for all children younger than 12 years of age (see **CONTRAINDICATIONS**).

- Acetaminophen and codeine phosphate tablets are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy (see **CONTRAINDICATIONS)** .

- Avoid the use of acetaminophen and codeine phosphate tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative

status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression (see **WARNINGS**).

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets slowly in geriatric patients and monitor closely for signs of central nervous system depression (see **WARNINGS**).

These drugs are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

- The following serious adverse reactions are described, or described in greater detail, in other sections:
- Addiction, Abuse, and Misuse (see **WARNINGS**)
- Life-Threatening Respiratory Depression (see **WARNINGS**)
- Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children (see **WARNINGS**)
- Neonatal Opioid Withdrawal Syndrome (see **WARNINGS**)
- Interactions with CNS Depressants (see **WARNINGS**)
- Severe Hypotension (see **WARNINGS**)
- Gastrointestinal Adverse Reactions (see **WARNINGS**)
- Seizures (see **WARNINGS**)
- Withdrawal (see **WARNINGS**)

The following adverse reactions associated with the use of codeine were identified in postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious adverse reactions associated with codeine are respiratory depression and, to a

lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

The most frequently observed adverse reactions with codeine administration include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, sweating, and constipation.

Other adverse reactions include allergic reactions, euphoria, dysphoria, abdominal pain, pruritus, rash, thrombocytopenia, and agranulocytosis.

Other less frequently observed adverse reactions expected from opioid analgesics, including acetaminophen and codeine phosphate tablets:

Cardiovascular system: faintness, flushing, hypotension, palpitations, syncope.

Digestive System: abdominal cramps, anorexia, diarrhea, dry mouth, gastrointestinal distress, pancreatitis.

Nervous system: anxiety, drowsiness, fatigue, headache, insomnia, nervousness, shakiness, somnolence, vertigo, visual disturbances, weakness.

Skin and Appendages: rash, sweating, urticarial.

- Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
- Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- Anaphylaxis: Anaphylaxis has been reported with ingredients contained in acetaminophen and codeine phosphate tablets.
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids (see **CLINICAL PHARMACOLOGY**).

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Acetaminophen and codeine phosphate tablets contain codeine. Codeine in combination with acetaminophen, is a Schedule III controlled substance.

Abuse

Acetaminophen and codeine phosphate tablets contain codeine, a substance with a high potential for abuse similar to other opioids, including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Acetaminophen and codeine phosphate tablets can be abused and are subject to misuse, addiction, and criminal diversion (see **WARNINGS**).

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

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

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful, or potentially 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 providers. “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

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

Acetaminophen and codeine phosphate 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 Acetaminophen and Codeine Phosphate Tablets

Acetaminophen and codeine phosphate tablets are for oral use only. Abuse of acetaminophen and codeine phosphate tablets poses a risk of overdose and death. The risk is increased with concurrent use of acetaminophen and codeine phosphate tablets with alcohol and other central nervous system depressants.

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

Dependence

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

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g.,

naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

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

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

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

OVERDOSAGE

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

Clinical Presentation

Codeine

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

Acetaminophen

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

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

Treatment of Overdose

Codeine

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 serious arrhythmias will require advanced life-support measures.

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 acetaminophen and codeine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to codeine overdose.

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

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

Acetaminophen

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation.

Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, (NAC) should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

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

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

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

Monitor patients closely for respiratory depression, especially within the first 24 to 72

hours of initiating therapy and following dosage increases with acetaminophen and codeine phosphate tablets and adjust the dosage accordingly (see **WARNINGS**).

Initial Dosage

Initiating Treatment with Acetaminophen and Codeine Phosphate Tablets

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine higher than 60 mg are associated with an increased incidence of adverse reactions and are not associated with greater efficacy.

The usual adult dosage is:

Acetaminophen and Codeine Phosphate Tablets (codeine 30 mg and acetaminophen 300 mg): Take 1 to 2 tablets every 4 hours as needed for pain.

	Single Doses (Range)	**Maximum 24-Hour Dose**
Codeine Phosphate	30 mg to 60 mg	360 mg
Acetaminophen	300 mg to 1,000 mg	4,000 mg

The prescriber must determine the number of tablets per dose, and the maximum number of tablets per 24 hours, based upon the above dosage guidance. This information should be conveyed in the prescription.

Conversion from Other Opioids to Acetaminophen and Codeine Phosphate 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 acetaminophen and codeine phosphate tablets. It is safer to underestimate a patient's 24-hour acetaminophen and codeine phosphate tablets dosage than to overestimate the 24-hour acetaminophen and codeine phosphate tablets dosage and manage an adverse reaction due to overdose.

Titration and Maintenance of Therapy

Individually titrate acetaminophen and codeine phosphate tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Safe Reduction or Discontinuation of Acetaminophen and Codeine Phosphate Tablets

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

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

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

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

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

HOW SUPPLIED

Acetaminophen and Codeine Phosphate Tablets, USP, **300 mg/30 mg** are white, round, flat, beveled edged tablets debossed “IP 33” on obverse and “3” on reverse.

They are available as follows:

Bottles of 100:	NDC 65162-033-10
Bottles of 500:	NDC 65162-033-50
Bottles of 1000:	NDC 65162-033-11

Store Acetaminophen and Codeine Phosphate Tablets, USP 300 mg/30 mg between 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant container as defined in the USP.

Store acetaminophen and codeine phosphate tablets securely and dispose of properly (see **PRECAUTIONS; Information for Patients/Caregivers**).

Manufactured by:
Amneal Pharmaceuticals of NY, LLC
Brookhaven, NY 11719

Rev. 11-2019-10

Medication Guide
Acetaminophen and Codeine Phosphate (a seet’ a min’ oh fen and koe’ deen fos’ fate) Tablets CIII

Acetaminophen and Codeine Phosphate Tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage mild to moderate 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 Acetaminophen and Codeine Phosphate Tablets:

- **Get emergency help right away if you take too much acetaminophen and codeine phosphate tablets (overdose)**. When you first start taking acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets. They could die from taking it. Selling or giving away acetaminophen and codeine phosphate tablets is against the law.
- Store acetaminophen and codeine phosphate tablets securely, out of sight and reach of children and in a location not accessible by others, including visitors to the home.

Important Information Guiding Use in Pediatric Patients:

- Do not give acetaminophen and codeine phosphate tablets to a child younger than 12 years of age.
- Do not give acetaminophen and codeine phosphate tablets to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.
- Avoid giving acetaminophen and codeine phosphate tablets to children between 12 to 18 years of age who have risk factors for breathing problems such as obstructive sleep apnea, obesity, or underlying lung problems.

Do not take Acetaminophen and Codeine Phosphate Tablets if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or narrowing of the stomach or intestines.
- previously had an allergic reaction to codeine or acetaminophen.

Before taking Acetaminophen and Codeine Phosphate 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.
- Have been told by your healthcare provider that you are a “rapid metabolizer” of certain medicines.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of acetaminophen and codeine phosphate tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended; may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Acetaminophen and codeine phosphate tablets with certain other medicines can cause serious side effects that could lead to death.

When taking Acetaminophen and Codeine Phosphate Tablets:

- Do not change your dose. Take acetaminophen and codeine phosphate tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 4 hours as needed. Do not take more than your prescribed dose. If you miss a dose, take your next dose when needed.
- Call your healthcare provider if the dose you are taking does not control your pain.
  - If you have been taking acetaminophen and codeine phosphate tablets regularly, do not stop taking acetaminophen and codeine phosphate tablets without talking to your healthcare provider.
  - Dispose of expired, unwanted, or unused acetaminophen and codeine phosphate tablets by taking your drug to an authorized DEA-registered collector or drug take-back program. If one is not available, you can dispose of acetaminophen and codeine phosphate tablets by mixing the product with dirt, cat litter, or coffee grounds; placing the mixture in a sealed plastic bag, and throwing the bag in your trash.

While taking Acetaminophen and Codeine Phosphate Tablets DO NOT:

- Drive or operate heavy machinery, until you know how acetaminophen and codeine phosphate tablets affect you. Acetaminophen and codeine phosphate 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 acetaminophen and codeine phosphate tablets may cause you to overdose and die.

The possible side effects of Acetaminophen and Codeine Phosphate 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.

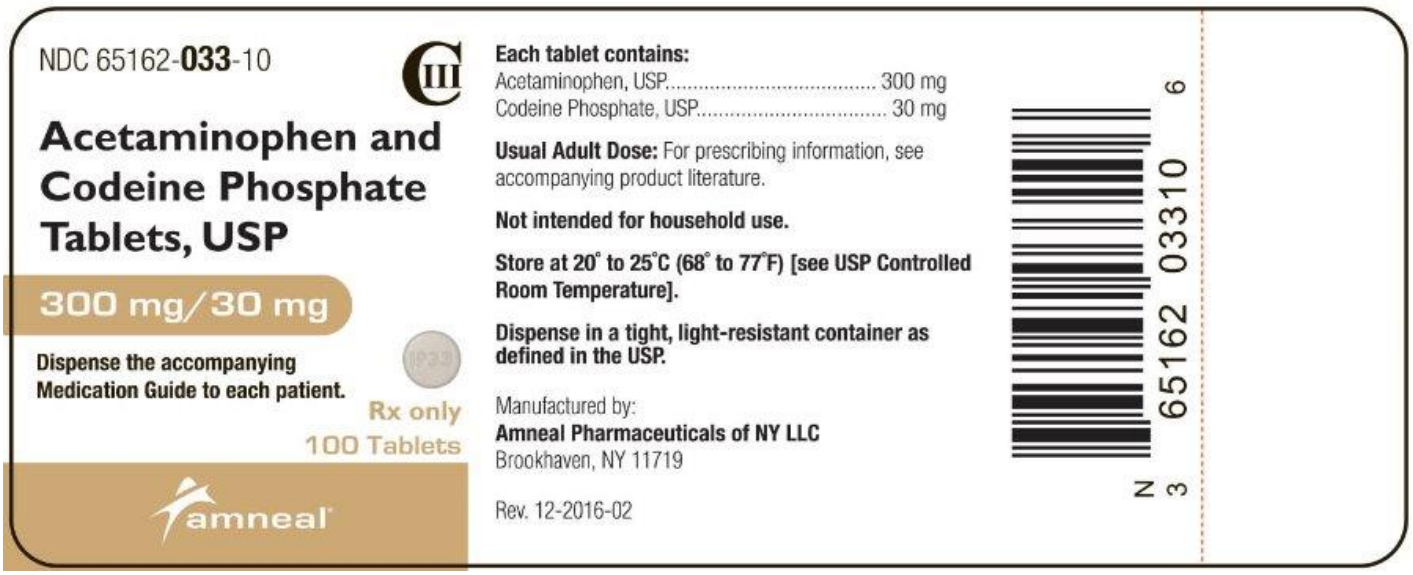
These are not all the possible side effects of acetaminophen and codeine phosphate tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov.

Manufactured by:
Amneal Pharmaceuticals of NY, LLC
Brookhaven, NY 11719

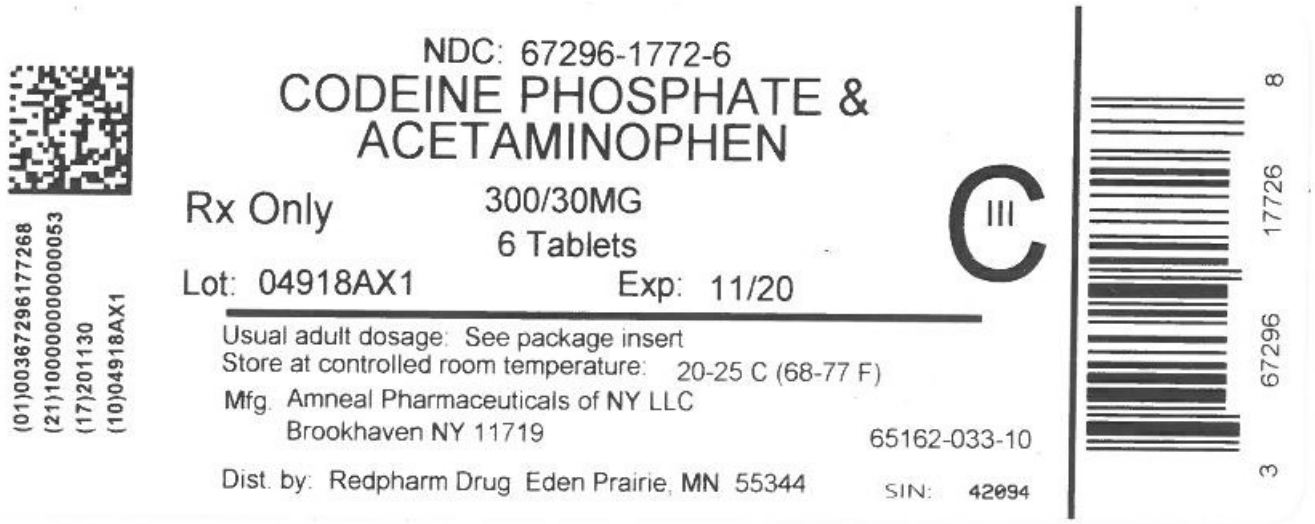
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Rev. 04-2019-08

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



ACETAMINOPHEN AND CODEINE

acetaminophen and codeine tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:67296-1772(NDC:65162-033)
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D)	ACETAMINOPHEN	300 mg
CODEINE PHOSPHATE (UNII: GSL05Y1MN6) (CODEINE ANHYDROUS - UNII:UX6OWY2V7J)	CODEINE PHOSPHATE	30 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
STARCH, CORN (UNII: O8232NY3SJ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
CROSPOVIDONE (UNII: 2S7830E561)	

Product Characteristics			
Color	white	**Score**	no score
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	IP33;3
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67296-1772-6	6 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2020	
2	NDC:67296-1772-1	10 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2020	
3	NDC:67296-1772-5	15 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/01/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040779	01/01/2020	

Labeler - RedPharm Drug, Inc. (828374897)

Establishment

Name	Address	ID/FEI	Business Operations
RedPharm Drug, Inc.		828374897	repack(67296-1772)

Revised: 4/2025 RedPharm Drug, Inc.