ACETAMINOPHEN AND CODEINE PHOSPHATE TABLETS, USP
Rx only

8182437 R12

ACETAMINOPHEN AND CODEINE PHOSPHATE TABLETS, USP
300 mg/15 mg CIII
Rx only

BOXED WARNING
WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATOTOXICITY; DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE 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 or conditions (see WARNINGS).

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

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).

Cytochrome P450 3A4 Interaction:
The concomitant use of acetaminophen and codeine phosphate tablets with all cytochrome P450 3A4 inhibitors may result in an increase in acetaminophen and codeine phosphate tablets plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in acetaminophen and codeine phosphate tablets plasma concentration. Monitor patients receiving acetaminophen and codeine phosphate tablets and any CYP3A4 inhibitor or inducer (see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions).

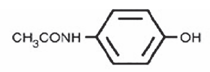
Hepatotoxicity:
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing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

Death Related to Ultra-Rapid Metabolism of Codeine to Morphine:
Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism (see WARNINGS, PRECAUTIONS).

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

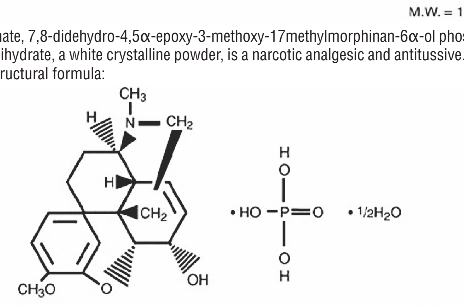
DESCRIPTION
Acetaminophen and codeine is supplied in tablet form for oral administration.

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:



$C_8H_9NO_2$ M.W. = 151.16

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



$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2H_2O$ M.W. = 406.37

Each 300 mg/15 mg Acetaminophen and Codeine Phosphate Tablet contains:
Acetaminophen .... 300 mg
Codeine Phosphate .... 15 mg

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

CLINICAL PHARMACOLOGY
This product combines the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen.

Pharmacokinetics:
The behavior on the individual components is described below.

Codeine:
Codeine is readily 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; however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

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.

See **OVERDOSAGE** for toxicity information.

Acetaminophen:
Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE
Acetaminophen and codeine phosphate tablets are indicated for the management of mild to moderately severe pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses (see **WARNINGS**), reserve acetaminophen and codeine phosphate tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics)
- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

CONTRAINDICATIONS
Acetaminophen and codeine phosphate tablets are contraindicated in:
- Patients with significant respiratory depression (see **WARNINGS**)
- Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (see **WARNINGS**)
- Postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy
- Patients who have previously exhibited hypersensitivity to codeine or acetaminophen

WARNINGS
Addiction, Abuse, and Misuse
Acetaminophen and codeine phosphate tablets contain codeine, 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 or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as 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**). Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

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

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of 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 24-72 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 even one dose of acetaminophen and codeine phosphate tablets, especially by children, can result in respiratory depression and death due to an overdose of codeine.

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. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see **PRECAUTIONS; Information for Patients, Pregnancy**).

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers
Concomitant use of acetaminophen and codeine phosphate tablets with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of acetaminophen and codeine phosphate tablets and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression (see **WARNINGS**), particularly when an inhibitor is added after a stable dose of acetaminophen and codeine phosphate tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in acetaminophen and codeine phosphate tablets-treated patients may increase acetaminophen and codeine phosphate tablets plasma concentrations and prolong opioid adverse reactions. When using acetaminophen and codeine phosphate tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in acetaminophen and codeine phosphate tablets-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of acetaminophen and codeine phosphate tablets until stable drug effects are achieved (see **PRECAUTIONS; Drug Interactions**).

Concomitant use of acetaminophen and codeine phosphate tablets with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease acetaminophen and codeine phosphate tablets plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to acetaminophen and codeine phosphate tablets. When using acetaminophen and codeine phosphate tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur (see **PRECAUTIONS; Drug Interactions**).

Risks 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 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** and **PRECAUTIONS; Information for Patients**).

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
The use of 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**).

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

Monitor such patients closely, particularly when initiating and titrating acetaminophen and codeine phosphate tablets and when acetaminophen and codeine phosphate tablets are given concomitantly with other drugs that depress respiration (see **WARNINGS**). Alternatively, consider the use of non-opioid analgesics in these patients.

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

Hepatotoxicity:
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

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

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

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

Death Related to Ultra-Rapid Metabolism of Codeine to Morphine
Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and 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). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine (see **PRECAUTIONS-Nursing Mothers**).

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. 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**).

Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see **CONTRAINDICATIONS**).

When prescribing codeine-containing products, 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**).

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

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Codeine is habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

PRECAUTIONS
General:
Acetaminophen and codeine phosphate tablets should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

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

Codeine may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product.

Advise patients that some people have a genetic variation that results in codeine changing into morphine more rapidly and completely than other people. Most people are unaware of whether they are an ultra-rapid codeine metabolizer or not. These higher-than-normal levels of morphine in the blood may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. Codeine-containing products are contraindicated in all children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving codeine-containing products for other reasons to monitor for signs of respiratory depression.

Nursing mothers taking codeine can also have higher morphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies. Instruct nursing mothers to watch for signs of morphine toxicity in their infants including increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Instruct nursing mothers to talk to the baby's doctor immediately if they notice these signs and, if they cannot reach the doctor right away, to take the baby to an emergency room or call 911 (or local emergency services).

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**). Instruct patients to take steps to store acetaminophen and codeine phosphate tablets securely. For disposal of unused acetaminophen and codeine phosphate tablets, advise patients to visit the DEA's website (http://www.deadiversion.usdoj.gov) or call 1-800-882-9539 for more information and to find an authorized collector in their community.

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

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

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

Pregnancy

Neonatal Opioid Withdrawal Syndrome
Inform patients 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, PRECAUTIONS; 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 nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs (see **PRECAUTIONS; Nursing Mothers**).

Disposal of Unused Acetaminophen and Codeine Phosphate Tablets
Advise patients to visit the DEA's website (http://www.deadiversion.usdoj.gov) or call 1-800-882-9539 for more information and to find an authorized collector in their community.

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

Drug Interactions:
CYP3A4
Inhibitor
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), can increase the plasma concentration of acetaminophen and codeine phosphate tablets, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of acetaminophen and codeine phosphate tablets and CYP3A4 inhibitors, 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, the acetaminophen and codeine phosphate tablets plasma concentration will decrease (see **CLINICAL PHARMACOLOGY**), resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to acetaminophen and codeine phosphate tablets.

If concomitant use is necessary, 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 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.

Medication Guide
ACETAMINOPHEN (a seet'' a min' oh fen) and CODEINE PHOSPHATE (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 moderately severe pain, severe enough to require an opioid analgesic, 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. Store acetaminophen and codeine phosphate tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away acetaminophen and codeine phosphate tablets is against the law.

Do not take acetaminophen and codeine phosphate tablets if you:
- have severe asthma, trouble breathing, or other lung problems.
- have a bowel blockage or have narrowing of the stomach or intestines.
- have known hypersensitivity to acetaminophen, codeine or any other component of this product.
- are a child, to treat pain after tonsillectomy and/or adenoidectomy.

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.

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.** Acetaminophen and codeine phosphate passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking 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.
- Take your prescribed dose at the same time every day. Doses may be repeated up to every 4 hours. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking acetaminophen and codeine phosphate tablets regularly, do not stop taking acetaminophen and codeine phosphate tablets without talking to your healthcare provider.
- After you stop taking acetaminophen and codeine phosphate tablets, dispose of unused tablets. Visit the

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- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage mild to moderately severe pain, severe enough to require an opioid analgesic, 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. Store acetaminophen and codeine phosphate tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away acetaminophen and codeine phosphate tablets is against the law.

Do not take acetaminophen and codeine phosphate tablets if you:
- have severe asthma, trouble breathing, or other lung problems.
- have a bowel blockage or have narrowing of the stomach or intestines.
- have known hypersensitivity to acetaminophen, codeine or any other component of this product.
- are a child, to treat pain after tonsillectomy and/or adenoidectomy.

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.

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. Acetaminophen and codeine phosphate passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking 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.
- Take your prescribed dose at the same time every day. Doses may be repeated up to every 4 hours. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking acetaminophen and codeine phosphate tablets regularly, do not stop taking acetaminophen and codeine phosphate tablets without talking to your healthcare provider.
- After you stop taking acetaminophen and codeine phosphate tablets, dispose of unused tablets. Visit the

Medication Guide
ACETAMINOPHEN (a seet'' a min' oh fen) and CODEINE PHOSPHATE (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 moderately severe pain, severe enough to require an opioid analgesic, 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.
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Job Info
Client: Par Pharmaceutical HT
Proof ID#: 227286-1
Date: 09/20/2016
Colors: K
Orientation: Head to Head - Front

Item# 8182437
Flat Size: 15.25" x 21.25"
Fold Size: 1.25" x 1.25"
Perforation: Dashed Line Perfs, Does Not Print
Misc:

Barcode Type 1: C128
Barcode Value 1: 8182437R12
Barcode Type 2:
Barcode Value 2:

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Proof Approval Form

Approval

Challenge Approval	Initials	Date	Customer Approval	Date
Artwork Set By:				
QA Approval:				

1. This electronic proof, for your written approval, is provided for purposes of indicating color break and image placement only, and not as a representation of color fidelity.
2. Barcode(s) provided on this proof is (are) for purposes of indicating encodation only and not to be used for grading according to ANSI standards, as applicable.

DEA's website (http://www.deadiversion.usdoj.gov) or call 1-800-882-9539 for more information and to find an authorized collector in your community.

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 for: **QUALITEST PHARMACEUTICALS, Huntsville, AL 35811** or call 1-800-444-4011

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

Issued: 9/2016
R2 8183823

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

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the acetaminophen and codeine phosphate tablets plasma concentration will increase (see **CLINICAL PHARMACOLOGY**), which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

If concomitant use is necessary, consider increasing the acetaminophen and codeine phosphate tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider acetaminophen and codeine phosphate tablets dosage reduction and monitor for signs of respiratory depression.

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

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

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

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

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:
No adequate studies have been conducted in animals to determine whether acetaminophen and codeine have a potential for carcinogenesis or mutagenesis.

Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and Micronucleus test on mouse bone marrow.

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

Pregnancy
Teratogenic Effects: Pregnancy Category C:
Codeine:
A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogeneses 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 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 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 and 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, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Nursing Mothers
Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine-containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding (see **WARNINGS-Death Related to Ultra-Rapid Metabolism of Codeine to Morphine**).

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

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

Pediatric Use:
Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme CYP2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see **CONTRAINDICATIONS** and **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 (see **WARNINGS**).

ADVERSE REACTIONS
Postmarketing Experience
- serotonin syndrome
- adrenal insufficiency

Androgen deficiency
Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms of hypogonadism, such as impotence, erectile dysfunction, or amenorrhea. The causal role of opioids in the syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

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

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

At higher doses codeine has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE
Controlled Substance:
Acetaminophen and codeine phosphate tablets contain codeine, 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 morphine and other opioids used in analgesia. 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, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

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

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

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

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

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.

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

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

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

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

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

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

In ***acetaminophen*** overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and coagulation defects may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment of Overdose
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 arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to acetaminophen and codeine phosphate tablets overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to acetaminophen and codeine phosphate tablets 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 re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

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

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

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with acetaminophen and codeine phosphate tablets and adjust the dosage accordingly (see **WARNINGS**).

Initial Dosage
Initiating Treatment with Acetaminophen and Codeine Phosphate Tablets
Initiate treatment with acetaminophen and codeine phosphate tablets in a dosing range noted below, as needed for pain. Doses may be repeated up to every 4 hours.

	Single Doses (range)	Maximum 24 Hour Dose
Codeine Phosphate	15 mg to 60 mg	360 mg
Acetaminophen	300 mg to 1000 mg	4000 mg

The usual dose of codeine phosphate in **children** is 0.5 mg/kg.

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.

Discontinuation of Acetaminophen and Codeine Phosphate Tablets
When a patient who has been taking acetaminophen and codeine phosphate tablets regularly and may be physically dependent no longer requires therapy with acetaminophen and codeine phosphate tablets, use a gradual downward titration of the dosage to prevent signs and symptoms of withdrawal. Do not stop acetaminophen and codeine phosphate tablets abruptly (see **WARNINGS, DRUG ABUSE AND DEPENDENCE**).

HOW SUPPLIED
Acetaminophen and Codeine Phosphate Tablets 300 mg/15 mg are white, round, flat-faced, beveled edge, scored (bisect bar) tablets, debossed "2063" and "V" on one side and debossed "2" on the reverse side. They are supplied in:

- Bottles of 100: NDC 0603-2337-21
- Bottles of 500: NDC 0603-2337-28
- Bottles of 1000: NDC 0603-2337-32

Dispense in a tight, light resistant container as defined in the USP/NF.
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Manufactured for:
QUALITEST PHARMACEUTICALS
Huntsville, AL 35811

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