DISCLAIMER

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ACETAMINOPHEN AND CODEINE PHOSPHATE ORAL SOLUTION, USP

Ⓒ V

Rx Only

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

Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering acetaminophen and codeine phosphate oral solution. Dosing errors due to confusion between mg and mL, and other codeine containing oral products of different concentrations can result in accidental overdose and death [see WARNINGS, DOSAGE AND ADMINISTRATION].

Addiction, Abuse, and Misuse

Acetaminophen and codeine phosphate oral solution exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing acetaminophen and codeine phosphate oral solution, and monitor all patients regularly for the development of these behaviors and conditions [see WARNINGS].

Life-Threatening Respiratory Depression

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

Accidental Ingestion

Accidental ingestion of acetaminophen and codeine phosphate oral solution, especially by children, can result in a fatal overdose of acetaminophen and codeine phosphate oral solution [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 an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism [see WARNINGS and PRECAUTIONS]. Codeine is contraindicated in children younger than twelve years of age and in children of any age who are undergoing tonsillectomy and/or adenoidectomy [see CONTRAINDICATIONS]. Avoid the use of acetaminophen and codeine phosphate oral solution 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 oral solution during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required 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 and PRECAUTIONS].

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].

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 oral solution 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 oral solution with all cytochrome P450 3A4 inhibitors or discontinuation of a cytochrome P450 3A4 inducer 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 oral solution 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 oral solution and any CYP3A4 inhibitor or inducer for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when acetaminophen and codeine phosphate oral solution are used in conjunction with inhibitors and inducers of CYP3A4 [see WARNINGS, PRECAUTIONS; Drug Interactions].

Cytochrome P450 2D6 Interaction

The concomitant use of acetaminophen and codeine phosphate oral solution with all cytochrome P450 2D6 inhibitors may result in an increase in codeine plasma concentrations and a decrease in the plasma concentration of the active metabolite, morphine, which could result in an analgesic efficacy reduction or symptoms of opioid withdrawal.

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

Follow patients receiving acetaminophen and codeine phosphate oral solution and any CYP2D6 inhibitor for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when acetaminophen and codeine phosphate oral solution are used in conjunction with inhibitors of CYP2D6 [see WARNINGS, PRECAUTIONS; Drug Interactions].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

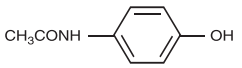
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see WARNINGS].

- **Reserve concomitant prescribing of acetaminophen and codeine phosphate oral solution 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

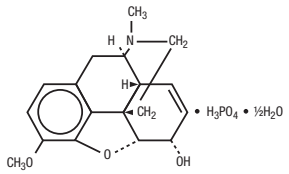
Acetaminophen and Codeine Phosphate Oral Solution is pharmacologically classified as an analgesic.

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-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate, a white crystalline powder, is an opiate agonist. It has the following structural formula:



$C_{18}H_{21}NO_3 \bullet H_3PO_4 \bullet ½\ H_2O$ M.W. = 406.37

Each Acetaminophen and Codeine Phosphate Oral Solution, USP 120 mg/12 mg per 5 mL, for oral administration, contains:

Acetaminophen.....120 mg
Codeine Phosphate.....12 mg
(Warning: May be habit-forming)
Alcohol.....7%

INACTIVE INGREDIENTS

Artificial cherry flavor, citric acid, FD&C Yellow No. 6, propylene glycol, purified water, saccharin sodium, sodium benzoate, and sucrose.

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 glucurodination 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 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 oral solution is 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 oral solution 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 oral solution is contraindicated in:

- Children less than 12 years of age [see **WARNINGS** and **PRECAUTIONS**].
- Postoperative pain management in children of any age who have undergone tonsillectomy and/or adenoidectomy [see **WARNINGS** and **PRECAUTIONS**].
- 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 [see **WARNINGS**].
- Patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see **WARNINGS**]
- Patients with hypersensitivity to codeine, acetaminophen, or any of the formulation excipients (e.g., anaphylaxis) [see **WARNINGS**].
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days.

WARNINGS

Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. Avoid dosing errors that may result from confusion between mg and mL and confusion with acetaminophen and codeine phosphate oral solution solutions of different concentrations, when prescribing, dispensing, and administering acetaminophen and codeine phosphate oral solution. Ensure that the dose is communicated clearly and dispensed accurately. A household teaspoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the risk of mistakenly using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that caregivers obtain and use a calibrated measuring device. Health care providers should recommend a calibrated device that can measure and deliver the prescribed dose accurately, and instruct caregivers to use extreme caution in measuring the dosage [see **WARNINGS**].

Addiction, Abuse, and Misuse

Acetaminophen and codeine phosphate oral solution contains codeine, a Schedule V controlled substance. As an opioid, acetaminophen and codeine phosphate oral solution exposes users to the risks of addiction, abuse, and misuse [see **DRUG ABUSE AND DEPENDENCE**].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed acetaminophen and codeine phosphate oral solution. 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 oral solution, and monitor all patients receiving acetaminophen and codeine phosphate oral solution 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 oral solution, but use in such patients necessitates intensive counseling about the risks and proper use of acetaminophen and codeine phosphate oral solution 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 oral solution. 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 oral solution, 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 oral solution.

To reduce the risk of respiratory depression, proper dosing and titration of acetaminophen and codeine phosphate oral solution are essential [see **DOSAGE AND ADMINISTRATION**]. Overestimating the acetaminophen and codeine phosphate oral solution 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 oral solution, especially by children, can result in respiratory depression and death due to an overdose of codeine.

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 postmarketing reports, children less 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 oral solution is contraindicated for all children younger than 12 years of age [see **CONTRAINDICATIONS**].
- Acetaminophen and codeine phosphate oral solution is contraindicated for postoperative pain management in pediatric patients of any age undergoing tonsillectomy and/or adenoidectomy [see **CONTRAINDICATIONS**].
- Avoid the use of acetaminophen and codeine phosphate oral solution 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 postoperative status, obstructive sleep apnea, obesity and other conditions associated with hypoventilation syndromes (e.g. neuromuscular disease), concomitant use of other medications that cause respiratory depression, and severe pulmonary disease.
- 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.

Nursing Mothers

A 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 oral solution.

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

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). Therefore, individuals who are ultra-rapid metabolizers should not use codeine.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of acetaminophen and codeine phosphate oral solution 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.

Risks of 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 oral solution 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 oral solution 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 oral solution 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 oral solution and any CYP3A4 inhibitor or inducer for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when acetaminophen and codeine phosphate oral solution are used in conjunction with inhibitors and inducers of CYP3A4 [see **WARNINGS, PRECAUTIONS; Drug Interactions**].

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

  The concomitant use of acetaminophen and codeine phosphate oral solution 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 oral solution and any CYP2D6 inhibitor for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when acetaminophen and codeine phosphate oral solution are used in conjunction with inhibitors of CYP2D6 [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 oral solution 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 oral solution is 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, Information for Patients, Drug Interactions**].

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

The use of acetaminophen and codeine phosphate oral solution 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 oral solution-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 oral solution [see **WARNINGS; Life-Threatening Respiratory Depression**].

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; Life-Threatening Respiratory Depression**].

Monitor such patients closely, particularly when initiating and titrating acetaminophen and codeine phosphate oral solution and when acetaminophen and codeine phosphate oral solution is 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 oral solution 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 phosphate oral solution may cause severe hypotension including 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 oral solution. In patients with circulatory shock acetaminophen and codeine phosphate oral solution may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of acetaminophen and codeine phosphate oral solution with circulatory shock.

Hepatotoxicity

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

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

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

Serious Skin Reactions

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

Hypersensitivity/Anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritis, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue acetaminophen and codeine phosphate oral solution immediately and seek medical care if they experience these symptoms. Do not prescribe acetaminophen and codeine phosphate oral solution for patients with acetaminophen allergy [see **PRECAUTIONS; Information for Patients/Caregivers**].

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 oral solution 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 oral solution.

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

Risks of Use in Patients with Gastrointestinal Conditions

Acetaminophen and codeine phosphate oral solution is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

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

Acetaminophen and codeine phosphate oral solution 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 oral solution 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 oral solution therapy.

Withdrawal

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 oral solution. In these patients, mixed agonist/antagonist and partial analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing acetaminophen and codeine phosphate oral solution, gradually taper the dosage [see **DOSAGE AND ADMINISTRATION**]. Do not abruptly discontinue acetaminophen and codeine phosphate oral solution [see **DRUG ABUSE AND DEPENDENCE**].

PRECAUTIONS

Risks of Driving and Operating Machinery

Acetaminophen and codeine phosphate oral solution 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 oral solution 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).

Medication Errors

Instruct patients how to measure and take the correct dose of acetaminophen and codeine phosphate oral solution, and ensure that the dose is communicated clearly and dispensed accurately. A household teaspoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the risk of using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that caregivers obtain and use a calibrated measuring device. Healthcare providers should recommend a calibrated device that can measure and deliver the prescribed dose accurately, and instruct caregivers to use extreme caution in measuring the dosage and when administering acetaminophen and codeine phosphate oral solution to ensure the dose is measured and administered accurately [see **WARNINGS**].

If the prescribed concentration is changed, instruct patients on how to correctly measure the new dose to avoid errors which could result in accidental overdose and death.

Addiction, Abuse, and Misuse

Inform patients that the use of acetaminophen and codeine phosphate oral solution, 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 oral solution with others and to take steps to protect acetaminophen and codeine phosphate oral solution 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 oral solution 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 oral solution securely. Advise patients to properly dispose of the acetaminophen and codeine phosphate oral solution in accordance with local state guidelines and/or regulations.

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

Advise patients that acetaminophen and codeine phosphate oral solution should not be used in children younger than 12 years of age or in a child of any age for pain treatment after tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 18 receiving codeine 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 oral solution is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these 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 of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers 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 oral solution while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking acetaminophen and codeine phosphate oral solution [see **WARNINGS, PRECAUTIONS; 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 oral solution [see **DOSAGE AND ADMINISTRATION**].

- Advise patients to always use a calibrated oral syringe/dosing cup when administering acetaminophen and codeine phosphate oral solution to ensure the dose is measured and administered accurately [see **WARNINGS**].
- Advise patients never to use household teaspoons or tablespoons to measure acetaminophen and codeine phosphate oral solution.
- Advise patients not to adjust the dose of acetaminophen and codeine phosphate oral solution without consulting with a physician or other healthcare professional.
- If patients have been receiving treatment with acetaminophen and codeine phosphate oral solution for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose as abrupt discontinuation of the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication [see **DOSAGE AND ADMINISTRATION**].

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 oral solution 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; Severe Hypotension**].

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in acetaminophen and codeine phosphate oral solution. Advise patients how to recognize such a reaction and to 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 oral solution 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 oral solution 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 oral solution [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 [see **ADVERSE REACTIONS**].

Driving or Operating Heavy Machinery

Inform patients that acetaminophen and codeine phosphate oral solution 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.

Disposal of Unused Acetaminophen and Codeine Phosphate Oral Solution

Advise patients to properly dispose of the acetaminophen and codeine phosphate oral solution. Advise patients to throw the drug in the household trash following these steps.

1. Remove them from their original containers and mix them with an undesirable substance, such as used coffee grounds or kitty litter (this makes the drug less appealing to children and pets, and unrecognizable to people who may intentionally go through the trash seeking drugs).
2. Place the mixture in a sealable bag, empty can, or other container to prevent the drug from leaking or breaking out of a garbage bag, or to dispose of in accordance with local state guidelines and/or regulations.

DRUG INTERACTIONS

CYP2D6 Inhibitors

Codeine is metabolized by CYP2D6 to form morphine. The concomitant use of acetaminophen and codeine phosphate oral solution and CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, bupropion, quinidine) can increase the plasma concentration of codeine, but decrease the plasma concentration of active metabolite morphine, particularly when an inhibitor is added after a stable dose of acetaminophen and codeine phosphate oral solution is achieved.

If concomitant use is necessary, consider dosage adjustment of acetaminophen and codeine phosphate oral solution until stable drug effects are achieved.

After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease but the morphine plasma concentration will increase. If a CYP2D6 inhibitor is discontinued, consider adjusting the acetaminophen and codeine phosphate oral solution dosage until stable drug achieved.

If concomitant use is necessary or if a CYP2D6 inhibitor is discontinued after concomitant use, monitor patients closely at frequent intervals. If signs and symptoms of respiratory depression or sedation occur, consider reducing the acetaminophen and codeine phosphate oral solution dosage until stable drug effects are achieved.

CYP3A4 Inhibitors

The concomitant use of acetaminophen and codeine phosphate oral solution 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 codeine, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of acetaminophen and codeine phosphate oral solution is achieved. If concomitant use is necessary, consider dosage reduction of acetaminophen and codeine phosphate oral solution until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to codeine. If a CYP3A4 inhibitor is discontinued, consider increasing the acetaminophen and codeine phosphate oral solution dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

CYP3A4 Inducers

The concomitant use of acetaminophen and codeine phosphate oral solution and CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) can decrease the plasma concentration of codeine, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to codeine. If concomitant use is necessary, consider increasing the acetaminophen and codeine phosphate oral solution dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the codeine plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression. If a CYP3A4 inducer is discontinued, consider acetaminophen and codeine phosphate oral solution 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, including alcohol, and 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 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 oral solution 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 oral solution 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, hydrocodone, 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 oral solution and/or precipitate withdrawal symptoms.

Advise patient to avoid concomitant use of these drugs.

Muscle Relaxants

Acetaminophen and codeine phosphate oral solution 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 oral solution 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 oral solution is 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 6000 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 1500 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: Pregnancy Category C

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 oral solution 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 oral solution is 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 oral solution, 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.

Lactation

Risk Summary

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 (one case) 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 the 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 oral solution (see **WARNINGS**).

Clinical Considerations

If infants are exposed to acetaminophen and codeine phosphate oral solution 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 breast-feeding is stopped.

Pediatric Use

The safety and effectiveness and the pharmacokinetics of acetaminophen and codeine phosphate oral solution 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** and **PRECAUTIONS**]. 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 oral solution is contraindicated for all children younger than 12 years of age [see **CONTRAINDICATIONS**].
- Acetaminophen and codeine phosphate oral solution is contraindicated for postoperative pain management in pediatric patients of any age undergoing tonsillectomy and/or adenoidectomy [see **CONTRAINDICATIONS**].

Avoid the use of acetaminophen and codeine phosphate oral solution 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 postoperative status, obstructive sleep apnea, obesity and other conditions associated with hypoventilation syndromes (e.g. neuromuscular disease), concomitant use of other medications that cause respiratory depression, and severe pulmonary disease [see **WARNINGS** and **PRECAUTIONS**].

Geriatric Use

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

To report SUSPECTED ADVERSE REACTIONS, contact Hi-Tech Pharmacal Co., Inc. at 1-800-262-9010 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Addiction, Abuse, and Misuse [see **WARNINGS**]
- Life-Threatening Respiratory Depression [see **WARNINGS**]
- Neonatal Opioid Withdrawal Syndrome [see **WARNINGS**]
- Ultra-rapid Metabolizers of Codeine [see **WARNINGS**]
- Interactions with CNS Depressants [see **WARNINGS**]
- Severe Hypotension [see **WARNINGS**]
- Gastrointestinal Adverse Reactions [see **WARNINGS**]
- Seizures [see **WARNINGS**]
- Withdrawal [see **WARNINGS**]

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, pruritis, rash, thrombocytopenia, and agranulocytosis.

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

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 oral solution.
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see **CLINICAL PHARMACOLOGY**].

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Acetaminophen and codeine phosphate oral solution contains codeine, a Schedule V controlled substance.

Abuse

Acetaminophen and codeine phosphate oral solution contains 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 oral solution can be abused and is subject to misuse, addiction, and criminal diversion [see **WARNINGS**].

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

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

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

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain

additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

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

Acetaminophen and codeine phosphate oral solution, 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 Oral Solution

Acetaminophen and codeine phosphate oral solution is for oral use only. Abuse of acetaminophen and codeine phosphate oral solution poses a risk of overdose and death. The risk is increased with concurrent use of acetaminophen and codeine phosphate oral solution 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 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 (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.

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

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

OVERDOSAGE

Following an acute overdosage, toxicity may result from 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. 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 codeine 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 phosphate oral solution overdose, administer an opioid antagonist. Only administer opioid antagonists in the presence of clinically significant respiratory, circulatory and/or central nervous system depression secondary to codeine overdose. In patients who are physically dependent on any opioid agonist including acetaminophen and codeine phosphate oral solution, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

Because the duration of opioid reversal is expected to be less than the duration of action of acetaminophen and codeine phosphate oral solution, 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.

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

Ensure accuracy when prescribing, dispensing, and administering acetaminophen and codeine phosphate oral solution to avoid dosing errors due to confusion between mg and mL, and with other acetaminophen and codeine phosphate oral solutions of different concentrations, which could result in accidental overdose and death. Ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume.

Ensure that the dose is communicated clearly and dispensed accurately. A household teaspoon or tablespoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the risk of using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that caregivers obtain and use a calibrated measuring device. Health care providers should recommend a calibrated device that can measure and deliver the prescribed dose accurately, and instruct caregivers to use extreme caution in measuring the dosage [see **WARNINGS**].

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 oral solution and adjust the dosage accordingly [see **WARNINGS**].

Initial Dosage

Initiating Treatment with Acetaminophen and Codeine Phosphate Oral Solution

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.

Acetaminophen and codeine phosphate oral solution contains 120 mg of acetaminophen and 12 mg of codeine phosphate per 5 mL (teaspoonful) and is given orally.

The recommended dose of codeine phosphate for children is 0.5 mg/kg body weight.

Children

(7 to 12 years): 10 mL (2 teaspoonfuls) 3 or 4 times daily.

(3 to 6 years): 5 mL (1 teaspoonful) 3 or 4 times daily.

(under 3 years): safe dosage has not been established.

Adults

15 mL (1 tablespoonful) every 4 hours as needed.

Conversion from Other Opioids to Acetaminophen and Codeine Phosphate Oral Solution

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 oral solution. It is safer to underestimate a patient's 24-hour acetaminophen and codeine phosphate oral solution dosage than to overestimate the 24-hour acetaminophen and codeine phosphate oral solution dosage and manage an adverse reaction due to overdose.

Titration and Maintenance of Therapy

Individually titrate acetaminophen and codeine phosphate oral solution to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving acetaminophen and codeine phosphate oral solution 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 oral solution 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 Oral Solution

When a patient who has been taking acetaminophen and codeine phosphate oral solution regularly and may be physically dependent no longer requires therapy with acetaminophen and codeine phosphate oral solution, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue acetaminophen and codeine phosphate oral solution in a physically dependent patient [see **WARNINGS, DRUG ABUSE AND DEPENDENCE**].

HOW SUPPLIED

Acetaminophen and Codeine Phosphate Oral Solution, USP is supplied in in 16 fl oz bottles, and 5 mL unit dose, 10 mL unit dose, 12.5 mL unit dose and 15 mL unit dose in tray of ten cups.

STORAGE

Store at 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

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

Manufactured by:
Hi-Tech Pharmacal Co., Inc.
Amityville, NY 11701

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