ACETAMINOPHEN AND CODEINE PHOSPHATE- acetaminophen and codeine phosphate tablet
Preferred Pharmaceuticals Inc.

Acetaminophen and Codeine Phosphate Tablets USP CIII

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF ACETAMINOPHEN AND CODEINE PHOSPHATE TABLETS

Addiction, Abuse, and Misuse
Because the use of 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 and reassess 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 tablets, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of acetaminophen and codeine phosphate tablets are essential (*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 (*see* WARNINGS).

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. 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 (*see* PRECAUTIONS, Drug Interactions).

Neonatal Opioid Withdrawal Syndrome (NOWS)
Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available (*see* WARNINGS).

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription (*see* WARNINGS).

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children
Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism (*see* WARNINGS, PRECAUTIONS; Information for Patients/Caregivers, Nursing Mothers). Acetaminophen and codeine phosphate tablets are contraindicated in children younger than 12 years

of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (*see* CONTRAINDICATIONS). Avoid the use of acetaminophen and codeine phosphate tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.

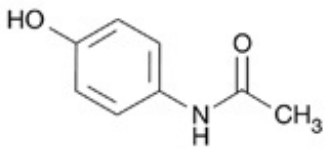
Interactions with Drugs Affecting Cytochrome P450 Isoenzymes
The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with acetaminophen and codeine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

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

DESCRIPTION

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

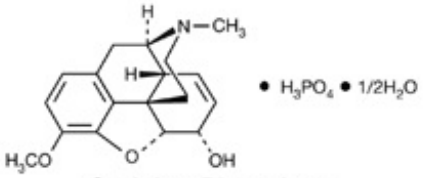
Acetaminophen, 4′-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



Acetaminophen

$C_8H_9NO_2$ MW = 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 a narcotic analgesic and antitussive. It has the following structural formula:



Codeine Phosphate

$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$ **MW = 406.37**

Each Acetaminophen and Codeine Phosphate Tablet USP (300 mg/15 mg) contains:

Acetaminophen USP……300 mg
Codeine Phosphate USP……15 mg

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

Acetaminophen USP……300 mg
Codeine Phosphate USP……30 mg

Each Acetaminophen and Codeine Phosphate Tablet USP (300 mg/60 mg) contains:

Acetaminophen USP……300 mg
Codeine Phosphate USP……60 mg

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

CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Pharmacodynamics

Effects on the Central Nervous System

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

Codeine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic

origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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

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.

Use of opioids for an extended period of time 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 opioid agonists. 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 (conjugation) and subsequent renal excretion of metabolites. Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways. Approximately 85% of an oral dose appears in the urine within
24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

Acetaminophen and codeine phosphate tablets are indicated for the management of mild to moderate pain, where treatment with an opioid is appropriate and for which alternative treatments are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy (*see* **WARNINGS**), reserve opioid analgesics, including acetaminophen and codeine phosphate tablets for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

CONTRAINDICATIONS

Acetaminophen and codeine phosphate tablets are contraindicated for:

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

Acetaminophen and codeine phosphate tablets are contraindicated in patients with:

- significant respiratory depression (*see* **WARNINGS**).
- acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (*see* **WARNINGS**).
- concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (*see* **WARNINGS**).
- known or suspected gastrointestinal obstruction, including paralytic ileus (*see* **WARNINGS**).
- hypersensitivity to codeine, acetaminophen, or any of the formulation excipients (e.g., anaphylaxis) (*see* **WARNINGS**).

WARNINGS

Addiction, Abuse, and Misuse

Acetaminophen and codeine phosphate tablets contain codeine. Codeine in combination with acetaminophen, is a Schedule III controlled substance. As an opioid, acetaminophen and codeine phosphate tablets expose users to the risks of addiction, abuse, and misuse (*see* **DRUG ABUSE AND DEPENDENCE**).

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed acetaminophen and codeine phosphate tablets. Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use (*see* **ADVERSE REACTIONS**).

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing acetaminophen and codeine phosphate tablets, and reassess all patients receiving acetaminophen and codeine phosphate tablets for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as acetaminophen and codeine phosphate tablets, but use in such patients necessitates intensive counseling about the risks and proper use of acetaminophen and codeine phosphate tablets along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider recommending or prescribing an opioid overdose reversal agent (*see* **WARNINGS, Life-Threatening Respiratory Depression; DOSAGE AND ADMINISTRATION, Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose**).

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. 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 careful storage of the drug during the course of treatment and proper disposal of unused drug. 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 overdose reversal agents, 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.

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

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

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose (*see* **PRECAUTIONS, Information for Patients/Caregivers**).

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent

fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper (*see* **DOSAGE AND ADMINISTRATION**).

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient (*see* **WARNINGS**).

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered (*see* **WARNINGS, OVERDOSAGE)**.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of acetaminophen and codeine phosphate tablets with benzodiazepines and/or other CNS depressants, including alcohol [e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), other opioids]. 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. Inform patients and caregivers of this potential interaction, educate them on the signs and symptoms of respiratory depression (including sedation).

If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent (*see* **WARNINGS, Life-Threatening Respiratory Depression; DOSAGE AND ADMINISTRATION, Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose**).

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* **Information for Patients/Caregivers**).

Neonatal Opioid Withdrawal Syndrome

Use of acetaminophen and codeine phosphate tablets for an extended period of time 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 an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (*see* **PRECAUTIONS, Information for Patients/Caregivers, Pregnancy**).

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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

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

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

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 younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the postoperative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

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

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

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

These individuals convert codeine into its active metabolite, morphine, more rapidly and

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

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

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

Cytochrome P450 3A4 Interaction

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

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

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

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

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

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

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

opioid withdrawal.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. Evaluate patients receiving acetaminophen and codeine phosphate tablets and any CYP2D6 inhibitor for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when acetaminophen and codeine phosphate tablets are used in conjunction with inhibitors of CYP2D6.

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

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

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

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4,000 milligrams of acetaminophen per day, even if they feel well.

Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect (**see Dependence**). Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safely switching the patient to a different opioid moiety) (**see DOSAGE AND ADMINISTRATION, WARNINGS**).

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

The use of acetaminophen and codeine phosphate tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease

Acetaminophen and codeine phosphate tablets-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of acetaminophen and codeine phosphate tablets (*see* **WARNINGS, Life-Threatening Respiratory Depression**).

Elderly, Cachectic, or Debilitated Patients

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

Regularly evaluate patients, 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.

Interaction with Monoamine Oxidase Inhibitors

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

Adrenal Insufficiency

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

Severe Hypotension

Acetaminophen and codeine may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced

blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) (*see* **PRECAUTIONS, Drug Interactions**). Regularly evaluate these patients for signs of hypotension after initiating or titrating the dosage of acetaminophen and codeine phosphate tablets. In patients with circulatory shock acetaminophen and codeine phosphate tablets may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of acetaminophen and codeine with circulatory shock.

Serious Skin Reactions

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

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

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), acetaminophen and codeine phosphate tablets may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with acetaminophen and codeine phosphate tablets.

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

Hypersensitivity/Anaphylaxis

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

Risks of Gastrointestinal Complications

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

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

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

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients

taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain) and, if necessary, adjust opioid therapy as clinically appropriate (*see***CLINICAL PHARMACOLOGY**).

Increased Risk of Seizures in Patients with Seizure Disorders

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

Withdrawal

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

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

PRECAUTIONS

Risks of Driving and Operating Machinery

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

Information for Patients/Caregivers

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

Storage and Disposal

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

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

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

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

Addiction, Abuse, and Misuse

Inform patients that the use of acetaminophen and codeine phosphate tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death (*see* **WARNINGS**). Instruct patients not to share acetaminophen and codeine phosphate tablets with others and to take steps to protect acetaminophen and codeine phosphate tablets from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting acetaminophen and codeine phosphate tablets or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose (*see* **WARNINGS, Life-Threatening Respiratory Depression**).

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death (*see* **WARNINGS**).

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if acetaminophen and codeine phosphate tablets are used with benzodiazepines or other CNS depressants, including alcohol (e.g., non-benzodiazepines, sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids), and not to use these drugs concomitantly unless supervised by a healthcare provider (*see* **WARNINGS** *and* **PRECAUTIONS, Drug Interactions**).

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of

CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) (*see* **WARNINGS, DOSAGE AND ADMINISTRATION)**.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that effects of opioid overdose reversal agents like naloxone and nalmefene are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if an opioid overdose reversal agent is administered (*see* **OVERDOSAGE)**.

Advise patients and caregivers:

- how to treat with the overdose reversal agent in the event of an opioid overdose.
- to tell family and friends about the opioid overdose reversal agent, and to keep it in a place where family and friends can access it in an emergency.
- to read the Patient Information (or other educational material) that will come with their opioid overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

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

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

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain (*see* **WARNINGS**; **ADVERSE REACTIONS**).

Serotonin Syndrome

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

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

MAOI Interaction

Inform patients not to take acetaminophen and codeine phosphate tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking

acetaminophen and codeine phosphate tablets (*see* **PRECAUTIONS, Drug Interactions**).

Important Administration Instructions

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

- Advise patients not to adjust the dose of acetaminophen and codeine phosphate tablets without consulting a physician or other healthcare professional.

Important Discontinuation Instructions

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

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.

Driving or Operating Heavy Machinery

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

Constipation

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

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**).

Hypotension

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

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in acetaminophen and codeine phosphate tablets. Advise patients how to recognize such a reaction, and if they develop signs of allergy such as a rash or difficulty breathing to

stop taking acetaminophen and codeine phosphate tablets and seek medical attention (*see* **CONTRAINDICATIONS** *and* **ADVERSE REACTIONS**).

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of acetaminophen and codeine phosphate tablets for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated (*see* **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 women that breastfeeding is not recommended during treatment with acetaminophen and codeine phosphate tablets (*see* **PRECAUTIONS, Nursing Mothers**).

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible (*see* **ADVERSE REACTIONS**).

Drug Interactions

CYP2D6 Inhibitors

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

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

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

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

After stopping use of a CYP2D6 inhibitor, consider reducing the acetaminophen and codeine phosphate tablets and evaluate the patient for signs and symptoms of

respiratory depression or sedation.

CYP3A4 Inhibitors

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

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

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

If a CYP3A4 inhibitor is discontinued, consider increasing the acetaminophen and codeine phosphate tablets dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal.

CYP3A4 Inducers

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

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

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

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

Benzodiazepines and Other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or

pregabalin), 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. Inform patients and caregivers of this potential interaction, educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent (*see* **WARNINGS**).

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. Examples of these drugs include, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and monoamine oxidase (MAO) inhibitors (used to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (*see* **PRECAUTIONS, Information for Patients/Caregivers**).

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

Monoamine Oxidase Inhibitors (MAOIs)

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

Advise patients taking acetaminophen and codeine phosphate tablets not to use MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses of other opioids (such as oxycodone, hydrocodone, oxymorphone, 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 tablets and/or precipitate withdrawal symptoms.

Advise patient to avoid concomitant use of these drugs.

Muscle Relaxants

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

If concomitant use is warranted, because respiratory depression may be greater than otherwise expected, decrease the dosage of acetaminophen and codeine phosphate tablets and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider recommending or prescribing an opioid overdose reversal agent (*see* **WARNINGS**).

Examples: Cyclobenzaprine, metaxalone.

Diuretics

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

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

Drug/Laboratory Test Interactions

Codeine may increase serum amylase levels.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Two-year carcinogenicity studies have been conducted in F344/N rats and B6C3F1 mice. There was no evidence of carcinogenicity in male and female rats, respectively, at dietary doses up to 70 and 80 mg/kg/day of codeine sulfate (approximately 2 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m^2 basis) for two years. Similarly there was no evidence of carcinogenicity activity in male and female mice at dietary doses up to 400 mg/kg/day of codeine sulfate (approximately 5 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m^2 basis) for two years.

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 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

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (*see* **ADVERSE REACTIONS**).

Pregnancy

Teratogenic Effects

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

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

Nonteratogenic Effects

Fetal/Neonatal Adverse Reactions
Use of opioid analgesics for an extended period of time 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 overdose reversal agent, such as naloxone or nalmefene, 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.

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

Nursing Mothers

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

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

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

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

Pediatric Use

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

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

- Acetaminophen and codeine phosphate tablets are contraindicated for all children younger than 12 years of age (*see* **CONTRAINDICATIONS**).
- Acetaminophen and codeine phosphate tablets are contraindicated for postoperative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy (*see* **CONTRAINDICATIONS**).
- Avoid the use of acetaminophen and codeine phosphate tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression (*see* **WARNINGS**).

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to acetaminophen and codeine phosphate tablets. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of acetaminophen and codeine phosphate tablets slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system depression (*see* **WARNINGS**).

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

ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse (*see* **WARNINGS**)
- Life-Threatening Respiratory Depression (*see* **WARNINGS**)
- Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children (*see* **WARNINGS**)
- Neonatal Opioid Withdrawal Syndrome (*see* **WARNINGS**)
- Interactions with CNS Depressants (*see* **WARNINGS**)
- Opioid-Induced Hyperalgesia and Allodynia (*see* **WARNINGS**)
- Severe Hypotension (*see* **WARNINGS**)
- Gastrointestinal Adverse Reactions (*see* **WARNINGS**)
- Seizures (*see* **WARNINGS**)
- Withdrawal (*see* **WARNINGS**)

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

Serious adverse reactions associated with codeine are respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

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

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

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

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

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

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

Skin and Appendages: rash, sweating, urticarial.

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

with opioid therapy of any duration (*see* **WARNINGS**).

- Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).
- Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term (*see* **WARNINGS**).

Adverse Reactions from Observational Studies

A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90 day period (n=978); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.

Over 12 months:

- approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
- approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse (defined in **DRUG ABUSE AND DEPENDENCE**), respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid-involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. New long-term use was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer

than the duration evaluated in the studies.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

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

Abuse

Acetaminophen and codeine phosphate tablets contain, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction (*see* **WARNINGS**).

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of acetaminophen and codeine phosphate tablets increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of acetaminophen and codeine phosphate tablets with alcohol and other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of acetaminophen and codeine phosphate tablets abuse include those with a history of prolonged use of any opioid, including products containing codeine, those with a history of drug or alcohol abuse, or those who use acetaminophen and codeine phosphate tablets in combination with other abused drugs.

“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 people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Acetaminophen and codeine phosphate tablets, like other opioids, can be diverted for nonmedical 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 reevaluation 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

Abuse of acetaminophen and codeine phosphate tablets poses a risk of overdose and death. The risk is increased with concurrent use of acetaminophen and codeine phosphate tablets with alcohol and/or other CNS 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 a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal 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 use.

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

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

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

OVERDOSAGE

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

Clinical Presentation

Codeine

Acute overdose 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, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations (*see* **CLINICAL PHARMACOLOGY**). Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Acetaminophen

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

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

Treatment of Overdose

Codeine

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

For clinically significant respiratory or circulatory depression secondary to acetaminophen and codeine overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

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

In an individual physically dependent on opioids, administration of the recommended usual dosage of the overdose reversal agent 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 reversal agent administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the reversal agent should be begun with care and by titration with smaller than usual doses of the reversal agent.

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

Acetaminophen and codeine phosphate tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.

Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals [see Warnings]. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of acetaminophen and codeine phosphate tablets for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.

Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.

There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient’s underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse (*see* **WARNINGS**).

Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with acetaminophen and codeine phosphate tablets. Consider this risk when selecting an initial dose and when making dose adjustments (*see* **WARNINGS**).

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there

are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient (*see* **WARNINGS; Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**).

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

Initial Dosage

Use of Acetaminophen and Codeine Phosphate Tablets as the First Opioid Analgesic
Initiate treatment with acetaminophen and codeine phosphate tablets in a dosing range of 300 mg to 600 mg of acetaminophen and 30 mg to 60 mg of codeine phosphate every 4 hours as needed for pain, at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of acetaminophen and codeine phosphate tablets.

The usual adult dosage is:
Acetaminophen and Codeine Phosphate Tablets (codeine 15 mg and acetaminophen 300 mg): Take 1 to 2 tablets every 4 hours as needed for pain.

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

Acetaminophen and Codeine Phosphate Tablets (codeine 60 mg and acetaminophen 300 mg): Take one tablet every 4 hours as needed for pain.

	Single Doses (Range)	**Maximum 24-Hour Dose**
Codeine Phosphate	15 mg to 60 mg	360 mg
Acetaminophen	300 mg to 1,000 mg	4,000 mg

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

Conversion from Other Opioids to Acetaminophen and Codeine Phosphate Tablets
There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of acetaminophen and codeine phosphate tablets. It is safer to underestimate a patient's 24-hour acetaminophen and codeine phosphate tablets dosage than to overestimate the 24-hour acetaminophen and codeine phosphate tablets dosage and manage an adverse reaction due to overdose.

Titration and Maintenance of Therapy

Individually titrate acetaminophen and codeine phosphate tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients

receiving acetaminophen and codeine phosphate tablets to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as reassessing 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 after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after dosage increase), consider reducing the dosage (*see* **WARNINGS**). Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Safe Reduction or Discontinuation of Acetaminophen and Codeine Phosphate Tablets

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

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

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

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs

and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

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

HOW SUPPLIED

Each Acetaminophen and Codeine Phosphate Tablet USP 300 mg/60 mg tablet contains acetaminophen 300 mg and codeine phosphate 60 mg. It is available as a round, white to off-white tablet debossed with “4” on one side and an M on the other side.

Bottles of 15..... NDC 68788-7859-1

Bottles of 20..... NDC 68788-7859-2

Bottles of 30..... NDC 68788-7859-3

Bottles of 60..... NDC 68788-7859-6

Store acetaminophen and codeine phosphate tablets at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

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

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

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SpecGx LLC
Webster Groves, MO 63119 USA

Rev 12/2025

Mallinckrodt™
Pharmaceuticals

An electronic copy of this medication guide can be obtained from www.mallinckrodt.com/Medguide/MG20A08.pdf or by calling 1-800-778-7898 for alternate delivery options.

Medication Guide

Acetaminophen and Codeine Phosphate Tablets USP, CIII
(a seet' a min' oh fen and koe' deen fos' fate)

Acetaminophen and codeine phosphate tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage mild to moderate pain, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed, you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about acetaminophen and codeine phosphate tablets:

- **Get emergency help or call 911 right away if you take too many 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. Ask your healthcare provider about medicines like naloxone or nalmefene that can be used in an emergency to reverse an opioid overdose.
- Taking acetaminophen and codeine phosphate tablets with other opioid medicines, benzodiazepines, gabapentinoids (gabapentin or pregabalin), alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma and death.
- Never give anyone else your acetaminophen and codeine phosphate tablets. They could die from taking it. Selling or giving away acetaminophen and codeine phosphate tablets is against the law.
- Store acetaminophen and codeine phosphate tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Important Information Guiding Use in Pediatric Patients:

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

Do not take acetaminophen and codeine phosphate tablets if you have:

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

Before taking acetaminophen and codeine phosphate tablets, tell your healthcare provider if you have a history of:

- head injury, seizures

- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems
- Have been told by your healthcare provider that you are a “rapid metabolizer” of certain medicines.

Tell your healthcare provider if you are:

- **noticing your pain getting worse.** If your pain gets worse after you take acetaminophen and codeine phosphate tablets, do not take more of acetaminophen and codeine phosphate tablets without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking acetaminophen and codeine phosphate tablets.
- **pregnant or planning to become pregnant.** Use of acetaminophen and codeine phosphate tablets for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended; may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs
- 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. Use the lowest dose possible for the shortest time needed.
- For acute (short-term) pain, you may only need to take acetaminophen and codeine phosphate tablets for a few days. You may have some acetaminophen and codeine phosphate tablets left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused acetaminophen and codeine phosphate tablets.
- Take your prescribed dose every 4 hours as needed for pain. 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.
    - Dispose of expired, unwanted, or unused acetaminophen and codeine phosphate tablets by taking your drug to an authorized DEA-registered collector or drug take-back program. If one is not available, you can dispose of acetaminophen and codeine phosphate tablets by mixing the product with dirt, cat litter, or coffee grounds; placing the mixture in a sealed plastic bag, and throwing the bag in your trash. Visit www.fda.gov/drugdisposal for

additional information on disposal of unused medicines.

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 or call 911 right away 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 healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov.

Manufactured by: SpecGx LLC, Webster Groves, MO 63119 USA,
www.mallinckrodt.com or call
1-800-778-7898

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

Issued: 12/2025
MG20A08

Mallinckrodt™

Repackaged By: Preferred Pharmaceuticals Inc.

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 300 mg/60 mg Bottle

NDC 68788-7859

Acetaminophen and Codeine Phosphate
Tablets USP

CIII

300 mg/60 mg

Each tablet contains:
Acetaminophen USP . . . . . 300 mg
Codeine Phosphate USP. . . . . 60 mg

Rx only

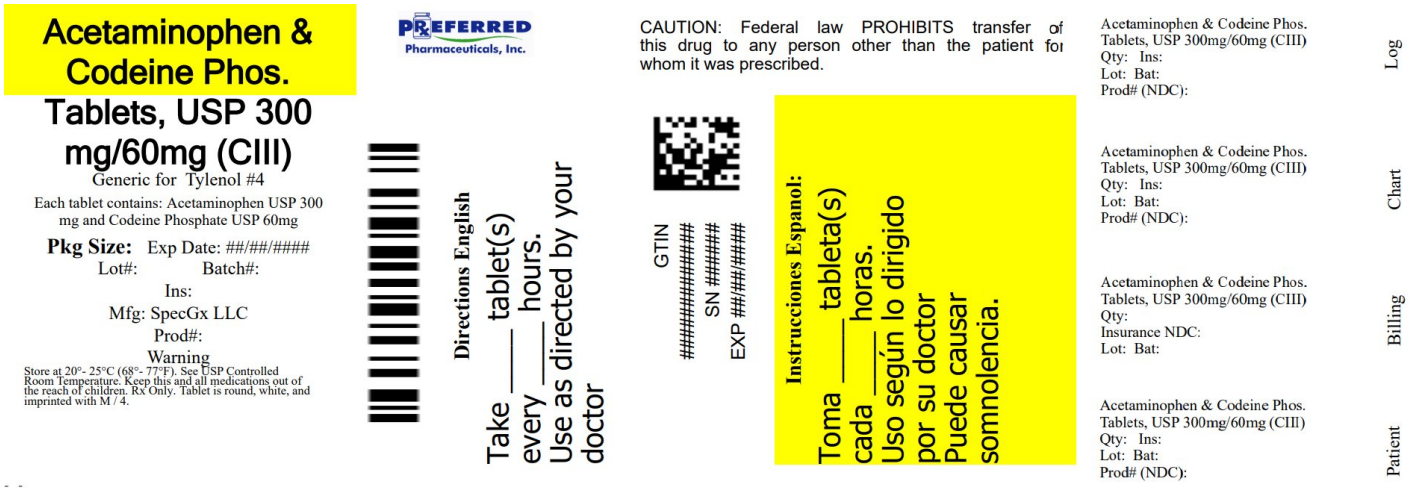
This package is not for household use.

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

Mallinckrodt™

L00A37
Rev 08/2017

Repackaged By: Preferred Pharmaceuticals Inc.



ACETAMINOPHEN AND CODEINE PHOSPHATE

acetaminophen and codeine phosphate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68788-7859(NDC:0406-0485)
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D)	ACETAMINOPHEN	300 mg
CODEINE PHOSPHATE (UNII: GSL05Y1MN6) (CODEINE ANHYDROUS - UNII:UX6OWY2V7J)	CODEINE PHOSPHATE	60 mg

Inactive Ingredients

Ingredient Name	Strength
CROSPOVIDONE (120 .MU.M) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
STARCH, CORN (UNII: O8232NY3SJ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

Product Characteristics

Color	WHITE (to off-white)	**Score**	no score
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	4;M
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68788-7859-1	15 in 1 BOTTLE; Type 0: Not a Combination Product	02/05/2021	
2	NDC:68788-7859-2	20 in 1 BOTTLE; Type 0: Not a Combination Product	02/05/2021	
3	NDC:68788-7859-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/05/2021	
4	NDC:68788-7859-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	02/05/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040419	02/05/2021	

Labeler - Preferred Pharmaceuticals Inc. (791119022)

Registrant - Preferred Pharmaceuticals Inc. (791119022)

Establishment

Name	Address	ID/FEI	Business Operations
Preferred Pharmaceuticals Inc.		791119022	REPACK(68788-7859)

Revised: 1/2026 Preferred Pharmaceuticals Inc.