

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION
^NCODEINE PHOSPHATE INJECTION USP

Codeine Phosphate

Solution for Injection 30mg/mL

USP

Opioid Analgesic–Antitussive

Sandoz Canada Inc.
110 Rue de Lauzon
Boucherville, QC, Canada
J4B 1E6

Date of Revision:
December 16, 2019

Submission Control No: 225996

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	13
DRUG INTERACTIONS	15
DOSAGE AND ADMINISTRATION	18
OVERDOSAGE	21
ACTION AND CLINICAL PHARMACOLOGY	22
STORAGE AND STABILITY	23
SPECIAL HANDLING INSTRUCTIONS	23
DOSAGE FORMS, COMPOSITION AND PACKAGING	24
PART II: SCIENTIFIC INFORMATION	25
PHARMACEUTICAL INFORMATION.....	25
PART III: CONSUMER MEDICATION INFORMATION.....	26

N¹CODEINE PHOSPHATE INJECTION USP

Codeine Phosphate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intramuscular, Subcutaneous	Solution for injection 30 mg/mL	Sodium metabisulfite 0.1% as preservative, hydrochloric acid and/or sodium hydroxide to adjust pH, and water for injection

INDICATIONS AND CLINICAL USE

Adults

Codeine Phosphate Injection USP is indicated for the symptomatic treatment of mild to moderate pain of various causes and the control of exhausting, nonproductive cough which does not respond to non-opioid antitussives.

Codeine Phosphate Injection USP is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (< 18 years of age)

The safety and efficacy of Codeine Phosphate Injection USP has not been studied in the pediatric population. The use of Codeine Phosphate Injection USP is not recommended in patients between 12 and 18 years of age, and is contraindicated in those under 12.

Contraindication in < 12 years old for any use

Regardless of the clinical setting, the use of codeine is contraindicated in patients below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see CONTRAINDICATIONS; and DOSAGE AND ADMINISTRATION).

Treatment for cough:

Codeine Phosphate Injection USP is not indicated for treatment of cough in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine and because the benefits of symptomatic treatment of cough.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance codeine phosphate or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- CYP2D6 ultra-rapid metabolizers who convert codeine into its active metabolite more rapidly and completely than other people (see WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-Rapid Metabolizers of Codeine; and OVERDOSAGE, Symptoms and Treatments)
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant or during labour and delivery (see Serious Warnings and Precautions, and WARNINGS AND PRECAUTIONS).
- Pediatric patients less than 12 years of age
- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, Codeine Phosphate Injection USP should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not

tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

Codeine Phosphate Injection USP poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Codeine Phosphate Injection USP, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Codeine Phosphate Injection USP should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of Codeine Phosphate Injection USP. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Codeine Phosphate Injection USP or following a dose increase.

Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental injection of even one dose of Codeine Phosphate Injection USP, especially by children, can result in a fatal overdose of codeine phosphate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of Codeine Phosphate Injection USP during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol

The ingestion of alcohol with Codeine Phosphate Injection USP should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

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

- Reserve concomitant prescribing of Codeine Phosphate Injection USP and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

General

Patients should be instructed not to give Codeine Phosphate Injection USP to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. Codeine Phosphate Injection USP should be stored securely to avoid theft or misuse.

Codeine Phosphate Injection USP should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Codeine Phosphate Injection USP as it may increase the chance of experiencing serious adverse events, including death. Patients should be instructed to stop use and consult a doctor if symptoms or cough worsen or persist for more than 7 days or if high fever, rash or persistent headache is present, as these may be signs of a serious condition.

Hyperalgesia that will not respond to a further dose increase of codeine phosphate can occur at particularly high doses. A codeine phosphate dose reduction or change in opioid may be required.

Patients should be counselled to discontinue codeine products and to seek urgent medical help at the earliest sign of codeine toxicity including symptoms such as confusion, shallow breathing, or extreme sleepiness which may be life threatening.

Abuse and Misuse

Like all opioids, Codeine Phosphate Injection USP is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Codeine Phosphate Injection USP should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Codeine Phosphate Injection USP, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Cardiovascular

Codeine phosphate administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Codeine Phosphate Injection USP.

The use of Codeine Phosphate Injection USP in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see DOSAGE AND ADMINISTRATION).

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Codeine Phosphate Injection USP and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Use in Drug and Alcohol Addiction

Codeine Phosphate Injection USP is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Codeine Phosphate Injection USP; extreme caution and awareness is warranted to mitigate the risk.

Endocrine

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one 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.

Gastrointestinal Effects

Codeine phosphate and other morphine-like opioids have been shown to decrease bowel motility.

Codeine phosphate may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see CONTRAINDICATIONS).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

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.

Use of Codeine Phosphate Injection USP is contraindicated in pregnant women (see CONTRAINDICATIONS).

Neurologic

Serotonin Syndrome: Codeine Phosphate Injection USP could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. antidepressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Codeine Phosphate Injection USP should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see DRUG INTERACTIONS).

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Codeine phosphate should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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 DRUG INTERACTIONS). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial

dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Codeine Phosphate Injection USP is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see DRUG INTERACTIONS).

Codeine Phosphate Injection USP should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see CONTRAINDICATIONS and ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury: The respiratory depressant effects of codeine phosphate, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, codeine phosphate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, codeine phosphate must be used with extreme caution and only if it is judged essential (see CONTRAINDICATIONS).

Risk of Death in Ultra-Rapid Metabolizers of Codeine

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. 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 labelled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. . (See Special Populations, Labour, Delivery and Nursing Women).

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and inform their patients about these risks and the signs of morphine overdose (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Peri-Operative Considerations

Codeine Phosphate Injection USP is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be

treated with Codeine Phosphate Injection USP for at least 24 hours before the operation and Codeine Phosphate Injection USP should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Codeine Phosphate Injection USP is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Codeine phosphate and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Codeine Phosphate Injection USP should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

Codeine Phosphate Injection USP may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of codeine phosphate with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Codeine phosphate should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Codeine Phosphate Injection USP, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Codeine Phosphate Injection USP and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of Codeine Phosphate Injection USP are essential. Overestimating the Codeine Phosphate Injection USP dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

Risk Factors for Life-threatening Respiratory Depression in Children

Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations).

- Codeine-containing products are contraindicated for all children younger than 12 years of age.
- Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome (see CONTRAINDICATIONS).
- Avoid the use of codeine-containing products 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.

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Codeine Phosphate Injection USP, as in these patients, even usual therapeutic doses of Codeine Phosphate Injection USP may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Codeine Phosphate Injection USP is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Codeine Phosphate Injection USP requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. (See **DRUG INTERACTIONS**)

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS**)

Special Populations

Special Risk Groups: Codeine phosphate should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, glaucoma, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in humans have not been conducted. Codeine Phosphate Injection USP crosses the placental barrier and is contraindicated in pregnant women.

Prolonged maternal use of *opioids* during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, can be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome)

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, Codeine Phosphate Injection USP is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Codeine Phosphate Injection USP is used in this population. Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. **However, some women are ultra-rapid metabolisers of codeine (see CONTRAINDICATIONS, Ultra-Rapid Metabolisers of Codeine; and WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-rapid Metabolizers of Codeine). These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breast-fed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death in nursing infants.**

Since there is a risk of infant exposure to codeine and morphine through breast milk, Codeine Phosphate Injection USP is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breast-feeding.

Pediatrics (< 18 years of age)

The safety and efficacy of Codeine Phosphate Injection USP has not been studied in the pediatric population. The use of Codeine Phosphate Injection USP is not recommended in patients between 12 and 18 years of age, and is contraindicated in those under 12.

Regardless of the clinical setting, the use of codeine is contraindicated in patients below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see CONTRAINDICATIONS and WARNINGS AND

PRECAUTIONS, Special Populations, Pediatrics; and DOSAGE AND ADMINISTRATION).

For Cough:

Codeine Phosphate Injection USP is not indicated for ~~use~~ treatment of cough in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine and because the benefits of symptomatic treatment of cough do not outweigh the risks for use of codeine in these patients (see also CONTRAINDICATIONS; and DOSAGE AND ADMINISTRATION).

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Patients with Hepatic Impairment:

Codeine phosphate should be given with caution and the initial dose should be reduced in patients with severe impairment of hepatic function.

Patients with Renal Impairment:

Codeine phosphate should be given with caution and the initial dose should be reduced in patients with severe impairment of renal function (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Patients with Renal Impairment).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of Codeine Phosphate Injection USP are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed adverse effects of Codeine Phosphate Injection USP are:

Major

Respiratory depression and respiratory arrest. To a lesser degree circulatory depression, shock and cardiac arrest (see WARNINGS and PRECAUTIONS).

Most Commonly Requiring Medical Attention

Sedation, nausea and vomiting, constipation and sweating. These effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated if the patient lies down.

Cardiovascular

Supraventricular tachycardia, bradycardia, palpitations, faintness, syncope, postural hypotension and hypertension, and phlebitis following i.v. injection.

CNS

Drowsiness, sedation, euphoria, dysphoria, weakness, headache, agitation, seizures, uncoordinated muscle movements, alterations of mood, dreams, hallucinations and disorientation, visual disturbances, insomnia, miosis, toxic psychoses.

Constipation

Practically all patients become constipated while taking opioid analgesics on a persistent basis. In some instances, particularly the elderly or bedridden, patients may become impacted. It is essential to caution patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged therapy.

Gastrointestinal

Dry mouth, nausea, vomiting, constipation, biliary tract spasm, laryngospasme, anorexia, diarrhea, cramps, dyspepsia, taste alterations.

Genitourinary

Urinary retention or hesitance, antidiuretic effect, reduced libido and/or potency.

Hypersensitivity

Pruritus, urticaria, other skin rashes, edema, diaphoresis, wheal and flare over the vein with IV injection. Because of close structural similarities, patients exhibiting systemic allergy to morphine (e.g., generalized rash, shortness of breath) should not receive codeine, diamorphine, hydromorphone, oxycodone or oxymorphone.

Withdrawal Syndrome

Physical dependence with or without psychological dependence tends to occur with chronic administration. An abstinence syndrome may be precipitated when an opioid analgesic is abruptly discontinued or opioid antagonists are administered. The following withdrawal symptoms may be observed after abrupt discontinuation of an opioid analgesic: body aches, diarrhea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, sleep disturbances, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use and gradual withdrawal from opioid analgesics, these symptoms are usually mild.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Other

Abnormal liver function test results (propoxyphene flushing/warmth).

Post-Marketing Experience

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

DRUG INTERACTIONS

Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants:

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). Codeine Phosphate Injection USP should not be consumed with alcohol as it may

increase the chance of experiencing dangerous side effects. The concurrent use of anticholinergic with codeine may produce paralytic ileus.

Interaction with Serotonin: Coadministration of codeine phosphate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

Drug-Drug Interactions

Anticholinergics

Concomitant use of drugs with antimuscarinic activity may increase the risk of severe constipation and/or urinary retention.

Cimetidine

Concurrent administration of cimetidine may lead to increased effect or toxicity of opioid analgesics.

CNS Agents

Concomitant administration of other CNS drugs such as sedatives, hypnotics, phenothiazines, anesthetics and alcohol may increase the sedative and depressant effects of opioid analgesics. If the concomitant use of these drugs is considered necessary, their doses should be reduced accordingly.

MAO Inhibitors

Serious adverse reactions have been reported in patients who receive MAO inhibitors with pethidine. Other opioid analgesics should be used with extreme caution, if at all, in patients taking MAO inhibitors (including selegiline) or within 14 days of such therapy.

Neuromuscular Blocking Agents

Opioid analgesics may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.

Opioid Antagonists

Naltrexone and agonist-antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol) should not be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist-antagonists may reduce the analgesic effect or may precipitate withdrawal symptoms.

Other Opioids

The use of more than one opioid agonist at a time is usually inappropriate; additive CNS depressant, respiratory depressant and hypotensive effects may occur if 2 or more agonists are used concurrently. Potentiation of effects may occur with a previously administered long-acting opioid analgesic.

Serotonergic Agents

Coadministration of codeine phosphate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see WARNINGS AND PRECAUTIONS).

Tricyclic Antidepressants

Tricyclic antidepressants may enhance opioid-induced respiratory depression.

Warfarin

Opioid agonists may potentiate the anticoagulant effects of coumarin anticoagulants.

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes :

The effects of concomitant use or discontinuation of CYP3A4 inducers, CYP3A4 inhibitors, or CYP2D6 inhibitors with codeine are complex, and requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

Avoid the use of Codeine Phosphate Injection USP while taking CYP3A4 inducers, CYP3A4 inhibitors, or CYP2D6 inhibitors. If concomitant use is necessary, monitor patients for respiratory depression and sedation at frequent intervals or for signs of opioid withdrawal.

CYP3A4 inhibitors: The concomitant use of Codeine Phosphate Injection USP and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), or protease inhibitors (e.g., ritonavir) can increase the plasma concentration of codeine and its subsequent metabolism by CYP2D6, resulting in greater morphine levels, which could increase or prolong opioid effects. The discontinuation of a concomitantly used CYP3A4 inhibitor might results in a reduced efficacy of Codeine Phosphate Injection USP.

CYP2D6 inhibitors: The concomitant use of Codeine Phosphate Injection USP and CYP2D6 inhibitors (e.g., amiodarone, quinidine) may result in a decrease in active metabolite morphine plasma concentration, leading to decreased efficacy or symptoms of opioid withdrawal. The discontinuation of a concomitantly used CYP2D6 inhibitor may lead to an increased metabolism to morphine, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

CYP3A4 inducers : The concomitant use of Codeine Phosphate Injection USP and CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, may result in a decreased plasma concentration of codeine and its active metabolite morphine, leading to decreased efficacy or symptoms of opioid withdrawal. The discontinuation of a concomitantly used CYP3A4 inducer can increase the plasma concentration of codeine and its active metabolite morphine which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

Drug-Laboratory Interactions

Opioid analgesics may interfere with certain diagnostic procedures, by increasing plasma amylase and lipase concentrations and by increasing CSF pressure. Gastric emptying is delayed by these drugs so gastric emptying studies will not be valid.

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION

Codeine Phosphate Injection USP should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

Pediatrics: (see also INDICATIONS)

Treatment of cough:

Codeine Phosphate Injection USP is not indicated for treatment of cough in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine and because the benefits of symptomatic treatment of cough do not outweigh the risks for use of codeine in these patients.

Contraindication in Children under 12, any use:

Regardless of clinical setting, codeine (including BRAND NAME) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see INDICATIONS)

Increasing Risk with Higher Doses

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. Each patient should be assessed for their risk prior to prescribing Codeine Phosphate Injection USP, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain or coughing should be assessed routinely to confirm the most appropriate dose and the need for further use of Codeine Phosphate Injection USP (see D&A - Adjustment or reduction of Dosage).

Dosing Considerations

Codeine Phosphate Injection USP should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

Recommended Dose and Dosage Adjustment

Codeine Phosphate Injection USP may be administered by subcutaneous or intramuscular injection.

Patients Not Receiving Opioids at the Time of Initiation of Codeine Treatment

Codeine, including Codeine Phosphate Injection USP, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 4 to 6 hours and not on scheduled intervals.

Analgesia

Adults: 30 to 60 mg every 4 to 6 hours.

Antitussive

As an antitussive agent, codeine is usually given orally.

Patients Currently Receiving Opioids

The approximate analgesic equivalences of various opioid analgesics, including codeine, can be determined from Table 1.

Opioid switching / rotation:

Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. Therefore, when switching from one opioid to another, **reduce calculated dose by 25-50%** to minimize the risk of overdose. Subsequently, up-titrate the dose as required to reach appropriate maintenance dose.

Table 1: OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES¹

Drug	Equivalent Dose (mg) ² (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10	60 ³	3-4
Oxycodone	15	30 ⁴	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine ⁶	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone ⁵	-	-	-
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4
Mixed Agonist-Antagonists⁷:			
Pentazocine ⁶	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

Footnotes:

¹References:

Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Foley KM. The treatment of cancer pain. *N Engl J Med* 1985;313(2):84-95.

Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. *Evaluation and treatment of chronic pain*. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.

Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. *Textbook of pain*. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

- ² **Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25% to 50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.[†] Upward titration may be required to reach appropriate maintenance doses.**

[†]Levy MH. Pharmacologic treatment of cancer pain. *N Engl J Med* 1996;335:1124-1132.

- ³ **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**

⁴ Based on single entity oral oxycodone in acute pain.

⁵ Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

⁶ Not recommended for the management of chronic pain.

⁷ Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Patients with Hepatic Impairment:

Codeine should be given with caution and the initial dose should be reduced in patients with severe impairment of hepatic function.

Patients with Renal Impairment:

Doses should be adjusted in renal failure, for creatinine clearance of 10 to 50 mL/min, decrease the dose by 25% and titrate. If creatinine clearance is less than 10 mL/min, decrease the dose by 50% and titrate.

Geriatrics:

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. Codeine Phosphate Injection USP should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Use with Non-Opioid Medications:

If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. Codeine Phosphate Injection USP can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration:

Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Codeine Phosphate Injection USP. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see WARNINGS AND PRECAUTIONS). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Disposal

Codeine Phosphate Injection USP should be kept in a safe place, out of the sight and reach of children before, during and after use. Codeine Phosphate Injection USP should not be used in front of children, since they may copy these actions.

Codeine Phosphate Injection USP should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired Codeine Phosphate Injection USP should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: May result in euphoria, dysphoria, visual disturbances, hypotension and coma or death from respiratory depression.

Treatment: Symptomatic and supportive therapy. Maintain ventilation and administer oxygen as needed. The opioid antagonist naloxone should be administered. If the patient is conscious and has not lost the gag reflex, empty the stomach by inducing emesis with ipecac syrup. If the patient is extremely drowsy, unconscious, convulsing or has no gag reflex, perform gastric lavage. Follow with activated charcoal (50 to 100 g in adults) and a cathartic.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Codeine exerts its effect on opiate receptors, primarily in the CNS and smooth muscle. Its effects include: analgesia, respiratory depression, suppression of the cough reflex, decreased gastrointestinal motility, CNS changes and stimulation of the chemoreceptor trigger zone which causes nausea and vomiting.

Pharmacodynamics

Central Nervous System:

Codeine phosphate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO₂ tension and to electrical stimulation.

Codeine phosphate depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Codeine phosphate 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 origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of codeine phosphate overdose.

Gastrointestinal Tract and Other Smooth Muscle:

Codeine phosphate 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 gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:

Codeine phosphate may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System:

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and

testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System:

In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics

Codeine is well absorbed from parenteral sites. Onset of analgesic action occurs in 10 to 30 minutes after parenteral administration. Peak effect is reached in 30 to 60 minutes after an IM or SC dose. Analgesia lasts 4 to 6 hours. Codeine's antitussive effect peaks within 1 to 2 hours and lasts up to 4 hours. Its plasma half-life is approximately 3 to 4 hours but may be as long as 19 hours in anephric patients. Codeine is approximately 7% bound to plasma protein; its volume of distribution is 2.5 to 3.5 L/kg.

Codeine is primarily metabolized by the liver, and its metabolites, some active, are eliminated in the urine. Only a small fraction (0.01) is excreted unchanged.

Special Populations and Conditions *(NOTE: this should not be underlined; according to the new template, it is a subheading of Pharmacokinetics. I propose to add this revision)*

Geriatrics:

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

Hepatic Impairment:

Codeine should be given with caution and the initial dose should be reduce in patients with severe impairment of hepatic function.

Renal Impairment:

Doses should be adjusted in renal failure, for creatinine clearance of 10 to 50 mL/min, decrease the dose by 25% and titrate. If creatinine clearance is less than 10 mL/min, decrease the dose by 50% and titrate.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from light.

Do not use the injection if it is more than slightly discoloured or if it contains a precipitate.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

Codeine Phosphate Injection USP is a colourless, sterile, aqueous solution containing 30 mg of codeine per mL, sodium metabisulfite 0.1% as preservative, hydrochloric acid and/or sodium hydroxide to adjust pH, and water for injection.

Packaging:

Codeine Phosphate Injection USP (30 mg/mL) is supplied in 1 mL ampoules, boxes of 10.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

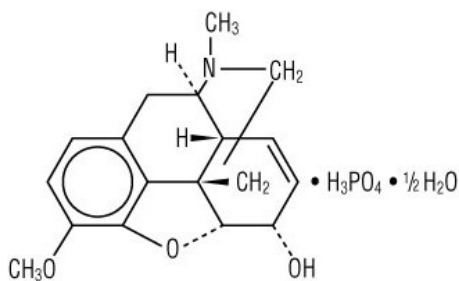
Proper name: Codeine Phosphate

Chemical name: Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, phosphate (1:1) (salt), hemihydrate, (5.alpha.,6.alpha.); Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5.alpha.,6.alpha.)-, phosphate (salt), hydrate (2:2:1)

Molecular formula: $C_{18}H_{21}NO_3 \cdot H_3O_4P \cdot \frac{1}{2} H_2O$

Molecular mass: 406.37g/mol

Structural formula:



Physicochemical Properties: White crystalline powder with a melting point at 235°C. Partially soluble in water.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**CODEINE PHOSPHATE INJECTION USP
Codeine Phosphate Solution for Injection**

Read this carefully before you start taking Codeine Phosphate Injection USP and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Codeine Phosphate Injection USP.

Serious Warnings and Precautions

- **Even if you take Codeine Phosphate Injection USP as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking Codeine Phosphate Injection USP. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your Codeine Phosphate Injection USP. They could die from taking it. If a person has not been prescribed Codeine Phosphate Injection USP, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took Codeine Phosphate Injection USP while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
 - **has changes in their breathing (such as weak, difficult or fast breathing)**
 - **is unusually difficult to comfort**
 - **has tremors (shakiness)**
 - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby.**
- **Taking Codeine Phosphate Injection USP with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is Codeine Phosphate Injection USP used for?

Codeine Phosphate Injection USP is an injection containing codeine (an opioid analgesic) used for:

- **Pain**
 - Codeine Phosphate Injection USP is used to manage pain in adults.
- **Cough**
 - Codeine Phosphate Injection USP is used to control cough in adults.
 - Codeine Phosphate Injection USP is not for treatment of cough in patients younger than 18 years of age. In patients this age, the risks of life-threatening breathing problems outweigh the benefits of treating the cough with codeine.

How does Codeine Phosphate Injection USP work?

Codeine Phosphate Injection USP is a painkiller and an antitussive belonging to the class of drugs known as opioids. It relieves pain and depresses the cough reflex by acting on specific nerve cells of the spinal cord and brain.

Codeine Phosphate Injection USP is used to treat mild to moderate pain in patients who need an opioid administered by injection and for the control of exhausting, nonproductive cough which does not respond to non-opioid antitussives. This is given under the skin or into the muscle.

What are the ingredients in Codeine Phosphate Injection USP?

Medicinal ingredients: codeine phosphate

Non-medicinal ingredients: hydrochloric acid and/or sodium hydroxide to adjust pH, sodium metabisulfite 0.1% as preservative, and water for injection

Codeine Phosphate Injection USP comes in the following dosage form:

Codeine Phosphate Injection USP (30 mg/mL) is supplied in 1 mL ampoules, boxes of 10.

Do not use Codeine Phosphate Injection USP if you:

- your doctor did not prescribe it for you
- are allergic to codeine or any of the other ingredients in Codeine Phosphate Injection USP
- can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- have severe asthma, trouble breathing, or other breathing problems
- have bowel blockage or narrowing of the stomach or intestines
- have severe pain in your abdomen
- have a head injury
- are at risk for having seizures
- suffer from alcoholism
- are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOI) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- are going to have a, or recently had, planned surgery
- have been told by your doctor that you break down codeine rapidly. This can lead to codeine overdose even at the usual adult dose
- are pregnant or planning to become pregnant or you are in labour

- are breastfeeding. The use of codeine-containing products while breast-feeding may harm your baby. If you breastfeed and take Codeine Phosphate Injection USP, seek immediate medical care for your baby if they are overly drowsy, sedated, have difficulty breast-feeding, have breathing difficulties, and are floppy (have decreased muscle tone). This is very serious for the baby and can lead to death. Tell the baby's doctor that you are breastfeeding and took Codeine Phosphate Injection USP.
- are less than 12 years old
- are less than 18 years old and are having (or have recently had) your tonsils or adenoids removed because of frequent interruption of breathing during sleep

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Codeine Phosphate Injection USP. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have persistent or chronic cough (as occurs with smoking), glaucoma, high blood pressure
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines

Other warnings you should know about:

Some people metabolize codeine at a much faster rate than the general population. This may lead to accidental overdose. Stop taking Codeine Phosphate Injection USP and seek immediate medical help if you start feeling confused, have shallow breathing, or extreme sleepiness. If you know that you metabolize codeine at a much faster rate, tell your doctor BEFORE starting this medication.

Stop taking Codeine Phosphate Injection USP and consult with your healthcare professional if:

- you get a high fever, rash or persistent headache while taking Codeine Phosphate Injection USP along with the cough.
- your symptoms or cough worsen or continue for more than 7 days.

These could be signs of a serious condition.

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence. As with all opioids,

taking codeine may cause you to become dependent on it. Do not take more than the dose prescribed to you by your doctor.

Breathing problems:

- Avoid taking Codeine Phosphate Injection USP if you are under 18 years of age and you are at risk for breathing problems because you:
- have obstructive sleep apnea
- are obese
- have an existing lung problem

Pregnancy, nursing, labour and delivery: Do not use Codeine Phosphate Injection USP while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. Codeine Phosphate Injection USP can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking Codeine Phosphate Injection USP, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking Codeine Phosphate Injection USP. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to Codeine Phosphate Injection USP. Codeine Phosphate Injection USP can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off Codeine Phosphate Injection USP.

Serotonin Syndrome: Codeine Phosphate Injection USP can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take Codeine Phosphate Injection USP with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;

- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Codeine Phosphate Injection USP:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Codeine Phosphate Injection USP. It can lead to:
 - drowsiness
 - unusually slow or weak breathing
 - serious side effects or
 - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by Codeine Phosphate Injection USP
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take Codeine Phosphate Injection USP with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin (such as coumadin) and other anticoagulants (used for prevention or treatment of blood clots)
- some anti-retroviral drugs (used to treat viral infections)
- some anti-fungal drugs (used to treat fungal infections)
- some antibiotic drugs (used to treat bacterial infections)
- some heart medication (such as beta blockers)
- tranquilizers, sedatives, sedating antihistamines, other depressants
- grapefruit juice
- drugs used to treat migraines (e.g. triptans)

- St. John's Wort

How to take Codeine Phosphate Injection USP:

- Codeine Phosphate Injection USP may be administered by subcutaneous or intramuscular injection.
- Codeine Phosphate Injection USP should not be used in children less than 12 years old.
- Codeine, including Codeine Phosphate Injection USP, should be prescribed at the lowest effective dose for the shortest period of time.-Dosing should be as needed every 4 to 6 hours and not on scheduled intervals.

Usual Adult Starting Dose:

Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. Higher doses and longer use can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need Codeine Phosphate Injection USP. Be sure to use Codeine Phosphate Injection USP only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking Codeine Phosphate Injection USP, tell your doctor immediately.

Stopping your Medication

If you have been taking Codeine Phosphate Injection USP for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking Codeine Phosphate Injection USP. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness

- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking Codeine Phosphate Injection USP.

Refilling your Prescription for Codeine Phosphate Injection USP:

A new written prescription is required from your doctor each time you need more Codeine Phosphate Injection USP. Therefore, it is important that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much Codeine Phosphate Injection USP, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using Codeine Phosphate Injection USP?

These are not all the possible side effects you may feel when taking Codeine Phosphate Injection USP. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- drowsiness
- insomnia
- dizziness
- fainting
- nausea, vomiting, or a poor appetite
- dry mouth
- headache
- problems with vision

- weakness, uncoordinated muscle movement
- itching
- sweating
- constipation
- low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using Codeine Phosphate Injection USP.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE:			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin			✓
Respiratory Depression: Slow, shallow or weak breathing			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations		✓	
Low Blood Pressure: dizziness, fainting, light-headedness	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired Codeine Phosphate Injection USP in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep Codeine Phosphate Injection USP under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Codeine Phosphate Injection USP, get emergency help right away.**
- Store between 15 and 30°C. Protect from light.

Disposal:

Codeine Phosphate Injection USP should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about Codeine Phosphate Injection USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the [Health Canada website \(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html\)](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sandoz.ca, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Last Revised: December 16, 2019