PRESCRIBING INFORMATION

INCLUDING PATIENT MEDICATION INFORMATION

[N] PROCET-30

Acetaminophen and Codeine Phosphate Tablets USP

300 mg/30 mg

Analgesic – Antipyretic – Antitussive

PRO DOC LTÉE
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H7L 3W9

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TABLE OF CONTENTS

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Acetaminophen and Codeine Phosphate Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablet, 300 mg/30 mg	Colloidal Silicon Dioxide, Crospovidone, Lactose, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Sodium Starch Glycolate, Stearic Acid, Sunset Yellow FCF (FD&C Yellow No.6) Aluminium Lake and Talc.

INDICATIONS AND CLINICAL USE

Adults

PROCET-30 is indicated to provide enhanced analgesia in a wide variety of conditions requiring the control of moderate to severe, acute or chronic pain. It is also indicated as a non-salicylate analgesic / antipyretic / antitussive in acute colds and other acute respiratory diseases.

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 (< 12 years of age)

The safety and efficacy of acetaminophen and codeine phosphate tablets have not been studied in the pediatric population. Regardless of clinical setting, the use of codeine is contraindicated in patients below the age of 12 years due to increased safety concerns (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations**, **Pediatrics**).

CONTRAINDICATIONS

PROCET-30 is contraindicated in:

- Patients who are hypersensitive to the active substance acetaminophen and/or codeine phosphate, or other opioid analgesics or to any ingredients in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Prescribing Information.

- Patients with severe hepatic impairment or severe active liver disease.
- 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.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant or during labour and delivery.
- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome.
- Pediatric patients under 12 years old.

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, PROCET-30 (acetaminophen and codeine phosphate tablets) 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

PROCET-30 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 PROCET-30, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). PROCET-30 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 PROCET-30. 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 PROCET-30 or following a dose increase.

PROCET-30 must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving PROCET-30 can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental ingestion of even one dose of PROCET-30, especially by children, can result in a fatal overdose of acetaminophen and codeine phosphate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of PROCET-30 during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol

The co-ingestion of alcohol with PROCET-30 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 PROCET-30 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 PROCET-30 (acetaminophen and codeine phosphate) tablets to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. PROCET-30 should be stored securely to avoid theft or misuse.

PROCET-30 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 PROCET-30 as it may increase the chance of experiencing serious adverse events, including death.

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

Abuse and Misuse

Like all opioids, PROCET-30 is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, PROCET-30 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 PROCET-30, 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.

PROCET-30 is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

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 PROCET-30.

The use of PROCET-30 in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of PROCET-30 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

PROCET-30 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 PROCET-30; 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 did 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**).

Hepatic

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories, etc.). Do not exceed the maximum recommended daily dose of acetaminophen (see **DOSAGE AND ADMINISTRATION**).

As with any other non-prescription analgesic drug, physicians should be cognizant of and supervise the use of acetaminophen in patients with alcoholism, serious kidney or liver disease (see **CONTRAINDICATIONS**).

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports usually involve cases of

severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Physicians should alert their patients who regularly consume large amounts of alcohol not to exceed the recommended doses of acetaminophen.

Acetaminophen may cause hepatotoxicity in situations of intentional overdose (e.g., attempted suicide), unintentional overdose (e.g., overdosing when pain relief is not satisfactory), simultaneous use of multiple acetaminophen-containing preparations, accidental overdose or in very rare cases, after recommended doses, although causality has not been determined. The hepatotoxic reaction can be severe and life-threatening. Early symptoms following a hepatotoxic overdose may include nausea, vomiting, diaphoresis, lethargy, and general malaise. If appropriate treatment is not instituted, these may progress to upper quadrant pain, confusion, stupor, and sequelae of hepatic necrosis, such as jaundice, coagulation defects, hypoglycemia, and encephalopathy. Renal failure and cardiomyopathy may also occur. In the event of known or suspected overdosage, treatment with N-acetyl cysteine should be instituted immediately (see **OVERDOSAGE**), even when there are no obvious symptoms. Failure to promptly treat acetaminophen hepatotoxicity with N-acetyl cysteine can result in liver failure, leading to liver transplantation and/or death.

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 PROCET-30 is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic

Serotonin Syndrome: PROCET-30 could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. antidepressants, migraine medications). Treatment with the serotoninergic 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. PROCET-30 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): Acetaminophen and 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 antiemetics 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 PROCET-30 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**).

PROCET-30 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).**

Peri-Operative Considerations

PROCET-30 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 PROCET-30 for at least 24 hours before the operation and PROCET-30 should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if PROCET-30 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).

Acetaminophen and 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.

PROCET-30 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

PROCET-30 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 acetaminophen and 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 acetaminophen and codeine phosphate tablets, 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 PROCET-30 and following dose increases.
In patients with asthma or pulmonary emphysema, indiscriminate use may precipitate respiratory insufficiency resulting from increased viscosity of bronchial secretions and suppression of cough reflex.

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing elevated intracranial pressure. Furthermore, narcotics may produce side effects which can obscure the clinical course of patients with head injuries.

The administration of PROCET-30 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Use with caution in patients who have undergone thoracotomies or laparotomies, since suppression of the cough reflex may lead to retention of secretions postoperatively in these patients.

Codeine, including PROCET-30, is not recommended for use in any patient in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, lung infections, multiple trauma or extensive surgical procedures.

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 PROCET-30 are essential. Overestimating the PROCET-30 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**).

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

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 pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with PROCET-30, as in these patients, even usual therapeutic doses of PROCET-30 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 PROCET-30 is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

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, Post-Marketing Experience**).

Skin

Rarely, acetaminophen can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. It is important to recognize and react quickly to the initial symptoms of these reactions which may occur without warning but may be manifested by any serious skin reactions. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at their first appearance.

Special Populations

Special Risk Groups: Acetaminophen and 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, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

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 labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

Pregnant Women: Studies in humans have not been conducted. PROCET-30 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) (NOWS), ADVERSE REACTIONS, Post-Marketing Experience).**

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, PROCET-30 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 PROCET-30 is used in this population.

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

Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in breastfed infants are rare. However, some women are ultra-rapid metabolizers of codeine (see **WARNINGS AND PRECAUTIONS**, **Ultra-Rapid Metabolizers of Codeine**). These women achieve higher than expected serum levels of codeine's active metabolite, morphine, leading to higher than expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties and decreased tone, in their baby. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The prevalence of this CYP2D6*2x2 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and 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.

Newborns: Dependence and withdrawal signs have been reported in newborns whose mothers took opiates regularly during pregnancy. These signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. Signs usually appear during the first few days of life (see **CONTRAINDICATIONS**).

Pediatrics (< 12 years of age): The safety and efficacy of acetaminophen and codeine phosphate tablets have not been studied in the pediatric population. Regardless of clinical setting, the use of codeine is contraindicated in patients below the age of 12 years due to increased safety concerns (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

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:

Acetaminophen

PROCET-30 tablets are contraindicated in patients with severe hepatic impairment.

In patients with compromised liver function, acetaminophen could exacerbate liver insufficiency. The half-life of acetaminophen can be prolonged in patients with severe liver disease which could lead to increased exposure. Liver function should be monitored in patients with liver disease (see **Laboratory Tests**).

Patients with or without liver disease should not exceed the daily maximum dose of acetaminophen (4,000 mg). The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories etc.).

Codeine

In patients with hepatic impairment, pain control may be compromised because codeine may not be adequately metabolized. Alternative pain medication could be considered due to the possible insufficient analgesic effect.

Patients with Renal Impairment:

PROCET-30 tablets are contraindicated in patients with severe renal impairment.

Acetaminophen has been reported to cause toxicity in this population. Use of codeine is not recommended in patients with a Glomerular Filtration Rate (GFR) <30 mL/min. Patients with renal dysfunction have increased risk of toxicity. Renal function should be monitored in patients with renal disease (see **Laboratory Tests**).

Laboratory Tests

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of acetaminophen and codeine phosphate tablets 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 acetaminophen and codeine phosphate are gastrointestinal upset, drowsiness, nausea, vomiting and constipation.

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.

The following adverse effects occur less frequently with opioid analgesics, whether related or not to acetaminophen and codeine phosphate, are rash, urticaria, neutropenia, methemoglobinemia, thrombocytopenia, palpitations, pruritus, hyperhidrosis, agitation, and a slight increase in prothrombin time in patients receiving oral anticoagulants. Respiratory depression may be seen at higher doses, and the possibility of habituation or true addiction should be avoided.

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 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**).

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. Limited 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)**. PROCET-30 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.

Drug-Drug Interactions

Interaction with Anticoagulants: Patients who concomitantly medicate with warfarin-type anticoagulants and regular doses of acetaminophen have occasionally been reported to have unforeseen elevations in their international normalized ratio [INR]. Physicians should be cognizant of this potential interaction and monitor the INR in such patients closely while therapy is established. Many factors, including diet, medications, and environmental and physical states, may affect how a patient responds to anticoagulant therapy. There have been several reports that suggest that acetaminophen may produce hypoprothrombinemia (elevated INR or prothrombin time) when administered with coumarin derivatives. In other studies, prothrombin time did not change. Reported changes have been generally of limited clinical significance, however, periodic evaluation of prothrombin time should be performed when these agents are administered concurrently.

In the period immediately following discharge from the hospital or whenever other medications are initiated, discontinued, or taken regularly, it is important to monitor patient response to anticoagulation therapy with additional prothrombin time of INR determinations.

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

PROCET-30 should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

PROCET-30 must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving PROCET-30 can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

For acute pain, it is recommended that PROCET-30 be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that the maximum daily dosage of 12 tablets of PROCET-30 totaling 360 mg of codeine (54 morphine milligram equivalent) not be exceeded. Each patient should be assessed for their risk prior to prescribing PROCET-30, 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 should be assessed routinely to confirm the most appropriate dose and the need for further use of PROCET-30 (see D&A - Adjustment or reduction of Dosage).

Dosing Considerations

PROCET-30 should not be used in children less than 12 years old (see CONTRAINDICATIONS).

PROCET-30 (acetaminophen and codeine phosphate tablets) 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**).

PROCET-30 is not indicated for rectal administration. Dosing should be as needed every 6 hours and not on scheduled intervals.

PROCET-30 may be taken with or without food, with a glass of water.

Recommended Dose and Dosage Adjustment

Adults:

Take 1 tablet every 4-6 hours as required, do not exceed 12 tablets in 24 hours. If pain does not respond to 1 tablet, take 2 tablets at next dose.

Codeine, including PROCET-30, should be prescribed at the lowest effective dose for the shortest period of time. Dosage should be adjusted according to the severity of pain and the response of the patient. Acetaminophen with codeine is given orally. It should be kept in mind that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related.

Patients Not Receiving Opioids at the Time of Initiation of PROCET-30 Treatment

The usual initial adult dose is 1 to 2 tablets every 6 hours as required or as prescribed.

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. PROCET-30 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:

Do not co-administer with other drugs containing acetaminophen. PROCET-30 should not be used above the dosage recommended. **Overdose may result in severe or possibly fatal liver damage.**

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:

Because headache often involves a significant psychological component, a narcotic analgesic should only be employed for the treatment of headache when no other treatment is effective, in order to minimize the risk or psychological and physical dependence.

This product is inappropriate even in high doses for severe or intractable pain. Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain, but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects.

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including PROCET-30. 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.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with

advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

Disposal

PROCET-30 should be kept in a safe place, out of the sight and reach of children before, during and after use. PROCET-30 should not be used in front of children, since they may copy these actions.

PROCET-30 should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired PROCET-30 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.

Acetaminophen

Symptoms:

Serious hepatotoxicity may occur in adults after ingestion of a single dose of 10 g (150 mg/kg or greater) and fatalities have usually been reported after ingestion of a single dose of 15 g or more of acetaminophen.

Patients suffering from an overdose of acetaminophen will progress through 3 stages if untreated. During the first stage, which lasts from 12 to 24 hours, there may be anorexia, nausea, vomiting, diaphoresis and pallor. After 24 hours, earlier symptoms tend to abate and the patient may even feel well for one or a few days. Unfortunately, during this second phase, hepatic enzymes, serum bilirubin and prothrombin time begin to rise as hepatic necrosis progresses and tenderness may develop in the right upper quadrant. Three to 5 days after drug ingestion, the third phase sets in for those patients who develop significant hepatic necrosis. This phase is marked by the sequelae of hepatic necrosis which include jaundice, coagulation effects, hypoglycemia, encephalopathy as well as renal failure and myocardiopathy. Death occurs as a result of hepatic failure.

Treatment:

Large overdoses of acetaminophen are potentially fatal, unless an appropriate antidote such as N-acetylcysteine (NAC) is administered early after drug ingestion, usually within 12 to 16 hours.

There is some evidence to suggest that NAC may offer some protection even when given up to 24 hours after drug ingestion. The hepatotoxicity of acetaminophen is related to a secondary, reactive metabolite which is detoxified by conjugation with hepatic glutathione. A large overdosage of acetaminophen will result in an increased formation of the reactive metabolite which in turn may deplete stores of glutathione in the liver. Antidotes such as NAC probably act by restoring glutathione levels.

Emergency Procedure: The stomach should be emptied promptly.

Specific Therapy:

A careful estimate should be made of the quantity of acetaminophen ingested. Regardless of the quantity ingested, and particularly if it is estimated to be 7.5 g or more, an immediate loading dose of NAC should be administered if 24 hours or less have elapsed since drug ingestion. NAC is available as Mucomyst which contains a 20% solution of N-acetylcysteine in sterile vials of 10 and 30 mL. The 20% solution NAC in Mucomyst should be diluted to a 5% solution for oral administration, by using water, cola, grapefruit juice or orange juice. The diluted mixture should be consumed within 1 hour of preparation. The **loading dose** of NAC is 140 mg/kg of bodyweight. This should be followed by **maintenance doses** of 70 mg of NAC/kg of bodyweight, every 4 hours, for 17 doses. If the patient vomits within 1 hour of administration, the NAC dose should be repeated. If the patient is unable to tolerate oral administration, NAC should be administered i.v. (see the monographs for Mucomyst and Parvolex for detailed instructions). If activated charcoal has been used, lavage must be performed before initiating treatment with NAC.

Acetaminophen Plasma Assay: Acetaminophen plasma levels 4 hours post-ingestion of an overdose provide a fairly reliable prognostic indication of potential hepatotoxicity. Values of 200 µg/mL or more at 4 hours post-ingestion, or 50 µg/mL or more at 12 hours after ingestion, are associated with the possibility of hepatic toxicity. If the plasma levels of acetaminophen are more than 25% below these values, the risk of toxicity is much reduced.

Follow-Up and Supportive Therapy:

Monitoring of hepatic and renal function, and supportive measures, should be used as indicated. Hemodialysis or peritoneal dialysis has not been found helpful. Experience indicates that children under 5 years of age are more resistant than adults to the hepatic effects of acetaminophen overdose.

Codeine

Symptoms:

The primary symptoms due to overdosage of codeine include euphoria, dysphoria, visual disturbances, hypotension and coma or death due to respiratory depression.

Treatment:

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone, is a specific antidote for respiratory depression which may result

from an overdose or unusual sensitivity to narcotics. Therefore, an appropriate dose of naloxone should be administered, preferably by the i.v. route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of acetaminophen with codeine may exceed that of the antagonist, patients should be kept under continued surveillance and repeated doses of antagonists should be administered as needed to maintain adequate respiration. An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, i.v. fluids, vasopressors and other supportive measures should be employed as indicated.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Central Nervous System:

Acetaminophen and codeine phosphate tablets produce 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 CO_2 tension and to electrical stimulation.

Acetaminophen and codeine phosphate tablets depress 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.

Acetaminophen and codeine phosphate tablets cause 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:

Acetaminophen and codeine phosphate tablets cause 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:

Acetaminophen and codeine phosphate tablets 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.

Special Populations and Conditions

Pediatrics (< 12 years): Safety and efficacy of codeine in children has not been established and its use in this age group is contraindicated due to increased safety concerns (see **CONTRAINDICATIONS**).
Geriatrics: Use with caution in aged or debilitated patients.

STORAGE AND STABILITY

Store at 15 – 30°C. Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

Each non-homogenous orange, round, flat-faced bevel edge tablet engraved "PROCET-30" on one side and with a regular score on the other, contains: acetaminophen 300 mg and codeine phosphate 30 mg. Also contains as non-medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone, Lactose, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Sodium Starch Glycolate, Stearic Acid, Sunset Yellow FCF (FD&C Yellow No.6) Aluminium Lake and Talc. Gluten and tartrazine-free.

Packaging:

Available in HPPE bottles of 100 and 500.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

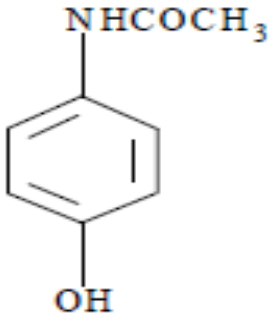
Drug Substance

Proper name: **Acetaminophen**

Chemical name: N-(4-Hydroxyphenyl) acetamide, 4'-hydroxyacetanilide

Molecular formula and molecular mass: $C_8N_9NO_2$, 151.2 g/mol

Structural formula:

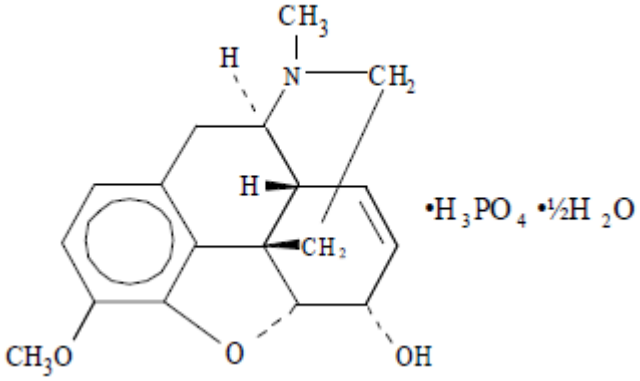


Proper name: **Codeine phosphate**

Chemical name: 7, 8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol-phosphate (1:1) (salt) hemihydrate

Molecular formula and molecular mass: $C_{18}H_{21}NO_3 \bullet H_3PO_4 \bullet ½H_2O$, 406.4 g/mol

Structural formula:



REFERENCES

1. Prescribing Information Including Patient Medication Information, TEVA-EMTEC-30 (acetaminophen and codeine phosphate tablets), Teva Canada Limited, Date of revision: May 24, 2018, Control No: 213748.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{N} PROCET-30

Acetaminophen and Codeine Phosphate Tablets USP

Read this carefully before you start taking PROCET-30 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 PROCET-30.

Serious Warnings and Precautions

- **Even if you take PROCET-30 as prescribed, you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take PROCET-30, it must be swallowed whole. Do not cut, break, crush, chew, dissolve the tablets. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking PROCET-30. 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 PROCET-30. They could die from taking it. If a person has not been prescribed PROCET-30, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took PROCET-30 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 PROCET-30 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 PROCET-30 used for?

PROCET-30 is used to manage your pain and as an alternative of non-aspirin type medication for acute colds and other acute respiratory diseases.

How does PROCET-30 work?

PROCET-30 is a painkiller belonging to the class of drugs known as opioids. It relieves pain by

acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in PROCET-30?

Medicinal ingredients: Acetaminophen and codeine phosphate

Non-medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone, Lactose, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Sodium Starch Glycolate, Stearic Acid, Sunset Yellow FCF (FD&C Yellow No.6) Aluminium Lake and Talc.

PROCET-30 comes in the following dosage forms:

Tablets: 300 mg acetaminophen and 30 mg codeine phosphate

Do not use PROCET-30 if:

- your doctor did not prescribe it for you
- you are allergic to acetaminophen or codeine phosphate or any of the other ingredients in PROCET-30
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale
- you have any heart problems
- you have severe liver problems or severe active liver disease
- you have suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you have severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOI) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding
- you 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
- you are under 12 years old

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PROCET-30. 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 heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your adrenal or prostate gland
- have, or had in the past, hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant

Other warnings you should know about:

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.

Pregnancy, nursing, labour and delivery: Do not use PROCET-30 while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. PROCET-30 can then cause life-threatening breathing problems in your unborn baby or nursing infant.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to PROCET-30. PROCET-30 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 PROCET-30.

Serotonin Syndrome: PROCET-30 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 PROCET-30 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.

Ultra-Rapid Metabolizers of Codeine:

Some individuals process codeine more rapidly and completely than others. This rapid processing in the body results in higher than expected drug levels. Even at the recommended doses, people whose bodies are ultra-rapid processors may have life-threatening or fatal effects on their breathing or experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

Drug Abuse and Dependence:

Codeine can produce drug dependence and has the potential for being abused. Tolerance, psychological and physical dependence may develop over time with repeated use of PROCET-30. Your healthcare professional should prescribe and administer PROCET-30 with the same degree of caution appropriate to the use of other oral opioid medications. Using these products for a prolonged period of time is not recommended.

Serious skin reactions (Stevens - Johnson Syndrome, Toxic Epidermal Necrolysis, Hypersensitivity Syndrome):

Acetaminophen can cause serious skin reactions that can spread to your mouth, lips, face, hands, trunk, arms and legs. This condition is life-threatening. Stop taking PROCET-30 and contact your healthcare professional immediately if you develop a rash during treatment (see table of **Serious side effects and what to do about them**, below).

Liver injury:

Taking acetaminophen in doses higher than recommended may result in liver injury, including

the risk of severe liver disease and death. Do not exceed the maximum recommended daily dose of acetaminophen including all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories etc.).

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 PROCET-30:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking PROCET-30. 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 PROCET-30
- 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 PROCET-30 with MAO inhibitors (MAOI) or if you have taken MAOIs in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- drugs used to treat migraines (e.g. triptans)
- antihistamines (drugs used to treat allergies)
- antiemetics (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)
- grapefruit juice
- St. John's Wort

How to take PROCET-30:

- usually 1 to 2 tablets every 6 hours, or as directed by your doctor.
- with a full glass of water

Do not take with other drugs containing acetaminophen.

Do not exceed the maximum recommended dose. Overdose may result in **severe or possibly fatal liver damage.**

Swallow whole. Do not cut, break, crush, chew or dissolve the tablets. This can be dangerous and can lead to death or seriously harm you.

Usual Adult Starting Dose:

Take 1 tablet every 4-6 hours as required, not to exceed 12 tablets in 24 hours. If pain does not respond to 1 tablet, take 2 tablets at next 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. It is recommended that you only take PROCET-30 for up to 7 days. If you need to take PROCET-30 for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses 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 PROCET-30. Be sure to use PROCET-30 only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking PROCET-30, tell your doctor immediately.

Stopping your Medication

If you have been taking PROCET-30 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 PROCET-30. You should check with your doctor for directions on how to slowly stop taking it. 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 PROCET-30.

Refilling your Prescription for PROCET-30:

A new written prescription is required from your doctor each time you need more PROCET-30. 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 PROCET-30, 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 PROCET-30?

These are not all the possible side effects you may feel when taking PROCET-30. 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 PROCET-30.

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 PROCET-30 in a secure place to prevent theft, misuse or accidental exposure.
- Store tablets at room temperature (15 – 30°C). Keep in a dry place.
- Keep PROCET-30 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 PROCET-30, get emergency help right away.

Disposal:

PROCET-30 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 PROCET-30:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient 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); or by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or info@prodoc.qc.ca.

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