PRESCRIBING INFORMATION

^{N}pms-ACETAMINOPHEN WITH CODEINE ELIXIR

Acetaminophen and Codeine Phosphate Oral Solution, USP

160 mg / 8 mg per 5 mL

Analgesic-Antipyretic

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montréal, Canada
H4P 2T4

www.pharmascience.com

Date of Revision:
July 28, 2020

Submission Control No.: 233489

PRESCRIBING INFORMATION

[N]pms-ACETAMINOPHEN WITH CODEINE ELIXIR

Acetaminophen and Codeine Phosphate Oral Solution, USP

Analgesic-Antipyretic

CLINICAL PHARMACOLOGY

Acetaminophen and codeine phosphate are analgesic, antipyretic agents.

ACTION

Acetaminophen and codeine phosphate combine the analgesic effects of the centrally acting analgesic codeine, with a peripherally acting analgesic, acetaminophen.

Acetaminophen and codeine phosphate are well absorbed orally. Acetaminophen is distributed throughout most tissues of the body. Acetaminophen is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral potency of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10% of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Pharmacokinetics

Following oral administration of acetaminophen in combination with codeine, both drugs are rapidly absorbed with peak plasma levels occurring within 60 minutes. Given two tablets (acetaminophen 300 mg, caffeine 15 mg and codeine 30 mg), acetaminophen 600 mg produces a peak plasma level of 6.25 μg/mL within 40 minutes, codeine phosphate 60 mg produces a peak plasma level of 150 ng/mL within 60 minutes

The plasma elimination half-life ($t_{1/2}$) ranges from 1.5 to 3.5 hours for acetaminophen, 1.5 to 4 hours for codeine. Metabolism is rapid; the principal metabolites are conjugates of glucuronic acid which are excreted in the urine. Less than 1% of an administered dose of codeine, and less than 4% of an administered dose of acetaminophen, is excreted unchanged in the urine.

Special Populations and Conditions

Geriatrics:
Elderly patients may be more susceptible to adverse effects, especially respiratory depression and constipation. Caution is advised; the initial dose should be reduced, and effects monitored. Elimination and metabolism may be slowed; lower doses or longer dosing intervals may be required.

INDICATIONS AND CLINICAL USE

pms-ACETAMINOPHEN WITH CODEINE ELIXIR (acetaminophen and codeine phosphate) oral solution is useful as an analgesic/antipyretic in the symptomatic treatment of mild to moderate pain and fever in adults.

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 **WARNINGS AND PRECAUTIONS**, **Special Populations, Geriatrics (> 65 years of age)**).

Pediatrics (< 18 years of age)
The safety and efficacy of pms-ACETAMINOPHEN WITH CODEINE ELIXIR has not been studied in the pediatric population. The use of pms-ACETAMINOPHEN WITH CODEINE ELIXIR is not recommended in patients between 12 and 18 years of age, and is contraindicated in those under 12 (see **WARNINGS AND PRECAUTIONS, Pediatrics**).

Contraindicated in < 12 years of age 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**).

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 **AVAILABILITY OF DOSAGE FORMS** section of the Prescribing Information.
- 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**).
- 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 <12 years of age.
- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnea 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, pms-ACETAMINOPHEN WITH CODEINE ELIXIR (acetaminophen and codeine phosphate) 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

pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-

ACETAMINOPHEN WITH CODEINE ELIXIR. 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR or following a dose increase.

Accidental Exposure

Accidental ingestion of even one dose of pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR (acetaminophen and codeine phosphate) to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. pms-ACETAMINOPHEN WITH CODEINE ELIXIR should be stored securely to avoid theft or misuse.

pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR as it may increase the chance of experiencing serious adverse events, including death.

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.

Patients should be counselled to keep this product out of the sight and reach of children.

Patients should be counselled to consult a physician if redness or swelling is present in an area of pain, if symptoms do not improve or if they worsen, or if new symptoms such as high fever, rash, itching, wheezing or persistent headache occur, as these may be signs of a condition which requires medical attention.

Acetaminophen should not be taken for pain for more than 5 days or for fever for more than 3 days, unless directed by a physician.

Patients should be counselled not to use with other products containing acetaminophen. Patients should be counselled to consult a physician before use if they are taking tranquilizers, sedatives, sedating antihistamines or other depressants, 3 or more alcoholic beverages per day, natural health products, prescription drugs, salicylates, any other pain and fever relief medication or nonsteroidal anti-inflammatory drugs (NSAIDS).

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 serious liver disease. 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.

Abuse and Misuse

Like all opioids, pms-ACETAMINOPHEN WITH CODEINE ELIXIR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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.

pms-ACETAMINOPHEN WITH CODEINE ELIXIR is intended for oral use only. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals on whether acetaminophen or codeine have a potential for carcinogenesis or mutagenesis. No adequate studies have been conducted in animals to determine whether acetaminophen has a potential for impairment of fertility.

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

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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR.

The use of pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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

pms-ACETAMINOPHEN WITH CODEINE ELIXIR is an acetaminophen/opioid combination product 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR; 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 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR is contraindicated in pregnant women (see **CONTRAINDICATIONS).**

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol):
pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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**).

pms-ACETAMINOPHEN WITH CODEINE ELIXIR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS; 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.

Serotonin toxicity / Serotonin syndrome:
Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with opioids, including pms-ACETAMINOPHEN WITH CODEINE ELIXIR, particularly during combined use with other serotonergic drugs (see **DRUG INTERACTIONS**).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with pms-ACETAMINOPHEN WITH CODEINE ELIXIR and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **DRUG INTERACTIONS**). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

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 labeled 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.

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

pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR for at least 24 hours before the operation and pms-ACETAMINOPHEN WITH CODEINE ELIXIR should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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.

pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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

pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR are essential. Overestimating the pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 apnea 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR, as in these patients, even usual therapeutic doses of pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Sleep Apnea: Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea (CSA) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion.

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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR

requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine (see **DRUG INTERACTIONS**).

Risks of Interactions with Warfarin:
Opioid agonists may potentiate the anticoagulant effects of coumarin anticoagulants (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, Post-Marketing Experience**).

Sensitivity
Serious Skin Reactions
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 the first appearance of skin rash or any other sign of hypersensitivity.

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, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

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

Codeine
There are no adequate and well controlled studies of codeine in pregnant or nursing 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, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome;** and **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.

Acetaminophen
There are no adequate and well-controlled clinical studies in pregnant or breastfeeding women for acetaminophen. Exercise caution when using acetaminophen during pregnancy.

When given to the mother in labeled doses, acetaminophen crosses the placenta into fetal circulation as early as 30 minutes after ingestion and is effectively metabolized by fetal sulfate conjugation.

Labour, Delivery and Nursing Women:
Since opioids can cross the placental barrier and are excreted in breast milk, pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 metabolizers of codeine** (see **CONTRAINDICATIONS;** 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, pms-ACETAMINOPHEN WITH CODEINE ELIXIR is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breast-feeding.

Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known.

Pediatrics (< 18 years of age):
The safety and efficacy of codeine has not been studied in the pediatric population. The use of pms-ACETAMINOPHEN WITH CODEINE ELIXIR is not recommended in patients between 12 and 18 years of age, and is contraindicated in those under 12.

Contraindicated in < 12 years of age 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**).

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**, **Special Populations and Conditions**, **Geriatrics**).

Patients with Hepatic Impairment:

Acetaminophen

pms-ACETAMINOPHEN WITH CODEINE is 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**).

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatoxicity and death. 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:

pms-ACETAMINOPHEN WITH CODEINE is contraindicated in patients with severe renal impairment, and acetaminophen has been reported to cause toxicity 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.

Codeine may increase serum amylase levels.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of pms-ACETAMINOPHEN WITH CODEINE ELIXIR(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 include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, and vomiting. These effects seem to be more prominent in ambulatory patients than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain, pruritus, rash, thrombocytopenia, and agranulocytosis. The incidence and severity of gastrointestinal upset is less than that after salicylate administration.

The classic gastrointestinal irritation associated with non-steroidal anti-inflammatory drugs, including ASA, does not occur with acetaminophen. Sensitivity reactions are rare and may manifest as rash or urticaria. Cross-reactivity in ASA-sensitive persons has been rarely reported. If sensitivity is suspected, discontinue use of the drug.

Adverse effects of codeine phosphate 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 are:

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.

Post-Marketing Experience:
Adverse drug reactions (ADRs) identified during post-marketing experience with codeine, acetaminophen or the combination are shown below according to their System Organ Class (SOC). The frequencies are estimated from spontaneous reports and sales data.

Gastrointestinal Disorders: (very rare) abdominal pain, dyspepsia.
Immune System Disorders: (very rare) anaphylactic reaction, hypersensitivity,
Investigations: (very rare) transaminases increased.
Nervous System Disorders: (very rare) headache, sedation
Psychiatric Disorders: (very rare) agitation, dependence, drug withdrawal syndrome, euphoric mood
Respiratory, Thoracic and Mediastinal Disorders: (very rare) bronchospasm, dyspnoea, respiratory depression
Vascular Disorders: (very rare) flushing
Skin and Subcutaneous Tissue Disorders: (very rare) angioedema, dermatitis, fixed eruption, pruritus, rash, urticaria, rash pruritic

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

Serious Drug Interactions

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

Overview

Interaction with Central Nervous System (CNS) Depressants:

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**). pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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

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.

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 Drugs:
Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5- HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (e.g. cyclobenzaprine), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Tricyclic Antidepressants:
Tricyclic antidepressants may enhance opioid-induced respiratory depression.

Warfarin:
Opioid agonists may potentiate the anticoagulant effects of coumarin 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.

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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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.

CYP2D6 inhibitors: The concomitant use of pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 inhibitors: The concomitant use of pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR.

CYP3A4 inducers: The concomitant use of pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 concomitantly used CYP3A4 inducers 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 Test 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

pms-ACETAMINOPHEN WITH CODEINE ELIXIR should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

Contraindication in Children under 12
Regardless of clinical setting, codeine (including pms-ACETAMINOPHEN WITH CODEINE ELIXIR**)** 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**).

For acute pain, it is recommended that pms-ACETAMINOPHEN WITH CODEINE ELIXIR be used for a maximum of 5 days at the lowest dose that provides adequate pain relief.

For fever, it is recommended that pms-ACETAMINOPHEN WITH CODEINE ELIXIR be used for a maximum of 3 days at the lowest dose that provides adequate fever relief.

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. The maximum recommended daily dose of pms-ACETAMINOPHEN WITH CODEINE ELIXIR is 100 mL, which is 160 mg codeine (24 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR (see **Recommended Dose and Dosage Adjustment,** below).

Dosing Considerations
pms-ACETAMINOPHEN WITH CODEINE ELIXIR (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**).

pms-ACETAMINOPHEN WITH CODEINE ELIXIR is not indicated for rectal administration.

pms-ACETAMINOPHEN WITH CODEINE ELIXIR is given orally.

pms-ACETAMINOPHEN WITH CODEINE ELIXIR may be taken with or without food, with a glass of water.

Codeine, including pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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.

Do not co-administer with other drugs containing acetaminophen.

The maximum recommended dose of pms-ACETAMINOPHEN WITH CODEINE ELIXIR should not be exceeded. Overdose may result in **severe or possibly fatal liver damage** (see **WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment**).

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine, higher than 60 mg, fail to give commensurate relief of pain but merely prolong analgesia, and are associated with an appreciably increased incidence of undesirable side effects.

Recommended Dose and Dosage Adjustment

Adults
10 mL to 20 mL every 4 -6 hours as required, not to exceed 5 doses in a 24- hour period.

Based on the dosage guidance, the number of mL per dose and the maximum number of doses per 24

hours should be conveyed in the prescription.

Patients with Hepatic Impairment:
Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatoxicity and death **(see WARNINGS AND PRECAUTIONS, Special Populations).** No dosage adjustment is recommended in patients with mild to moderate hepatic impairment. pms-ACETAMINOPHEN WITH CODEINE ELIXIR is contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**).

Patients with Renal Impairment:
No dosage adjustment is recommended in patients with mild to moderate renal impairment. pms-ACETAMINOPHEN WITH CODEINE ELIXIR is contraindicated in patients with severe renal impairment (see **CONTRAINDICATIONS**).

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. pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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:
See **DRUG INTERACTIONS**

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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR. 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.

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.

Disposal
pms-ACETAMINOPHEN WITH CODEINE ELIXIR should be kept in a safe place, out of the sight and reach of children before, during and after use. pms-ACETAMINOPHEN WITH CODEINE ELIXIR should not be used in front of children, since they may copy these actions.

pms-ACETAMINOPHEN WITH CODEINE ELIXIR should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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.

OVERDOSAGE

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

Acetaminophen:
Symptoms: Significant overdoses of acetaminophen may result in potentially fatal hepatotoxicity. The physician should be mindful that there is no early presentation that is pathognomonic for the overdose. A high degree of clinical suspicion must always be maintained.

Due to the wide availability of acetaminophen, it is commonly involved in single and mixed drug overdose situations and the practitioner should have a low threshold for screening for its presence in a patient's serum. Acute toxicity after single dose overdoses of acetaminophen can be anticipated when the overdose exceeds 150 mg/kg. Chronic alcohol abusers, cachectic individuals, and persons taking pharmacologic inducers of the hepatic P450 microsomal enzyme system may be at risk with lower exposures. Chronic intoxication has rarely been reported in persons consuming in excess of 150 mg/kg of acetaminophen daily for several days.

Symptoms:
Table 1 shows the clinical events associated with acetaminophen overdose that if seen with overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

Table 1: Adverse Drug Reactions Identified with Overdose of Acetaminophen

Metabolism and Nutrition Disorders:
Decreased appetite
Gastrointestinal Disorders:
Vomiting, Nausea, Abdominal discomfort
Hepatobiliary Disorders:
Hepatic necrosis, Acute hepatic failure, Jaundice, Hepatomegaly, Liver tenderness
General Disorders and Administration Site Conditions:
Pallor, Hyperhidrosis, Malaise
Investigations:
Blood bilirubin increased, Hepatic enzymes increased, International normalized ratio increased, Prothrombin time prolonged, Blood phosphorus increased, Blood lactic acid increased

The following clinical events listed in Table 2 are sequelae to acute hepatic failure and may be fatal. If these events occur in the setting of acute hepatic failure associated with acetaminophen overdose (adults and adolescents ≥ 12 years of age: > 7.5 g within 8 hours; children < 12 years of age: >150 mg/kg within 8 hours), they are considered expected.

Table 2: Expected Sequelae to Acute Hepatic Failure Associated with Acetaminophen Overdose

Infections and Infestations:
Sepsis, Fungal infection, Bacterial infection
Blood and Lymphatic System Disorders:
Disseminated intravascular coagulation, Coagulopathy, Thrombocytopenia
Metabolism and Nutrition Disorders:
Hypoglycemia, Hypophosphatemia, Metabolic acidosis, Lactic acidosis
Nervous System Disorders:
Coma (with massive acetaminophen overdose or multiple drug overdose), Encephalopathy, Brain edema
Cardiac Disorders:
Cardiomyopathy
Vascular Disorders:
Hypotension
Respiratory, Thoracic and Mediastinal Disorders:
Respiratory failure
Gastrointestinal Disorders:
Pancreatitis, Gastrointestinal hemorrhage
Renal and Urinary Disorders:
Acute kidney injury
General Disorders and Administration Site Conditions:
Multi-organ dysfunction syndrome

Blood and Lymphatic Disorders: Hemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Hemolysis has been reported in patients with G6PD deficiency,

with use of acetaminophen in overdose.

Treatment:
Specific Antidote: NAC (N-acetylcysteine) administered by either the intravenous or the oral route is known to be highly effective antidote for acetaminophen poisoning. It is most effective when administered within 8 hours of a significant overdose but reports have indicated benefits to treatment initiated well beyond this time period. It is imperative to administer the antidote as early as possible in the time course of acute intoxication to reap the full benefits of the antidote's protective effects.

General Management: When the possibility of acetaminophen overdose exists, treatment should begin immediately and include appropriate decontamination of the GI tract, proper supportive care, careful assessment of appropriately timed serum acetaminophen estimations evaluated against the Matthew-Rumack nomogram, timely administration of NAC as required and appropriate follow-up care. Physicians unfamiliar with the current management of acetaminophen overdose should consult with a poison control centre immediately. Delays in initiation of appropriate therapy may jeopardize the patient's chances of full recovery.

Codeine:
Symptoms: Risks of codeine overdose include asthenia, cardio-respiratory arrest, brain edema, coma, confusional state, seizure, drug dependence, fatigue, hypotension, hypoxia, ileus, miosis, renal failure, respiratory depression and respiratory failure, stupor, vomiting, and withdrawal syndrome.

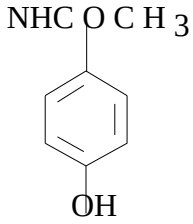
Typical Toxidrome: Narcotic/Opiate
Specific Antidote: Naloxone HCl

Treatment:
Stabilize the patient (A, B, C's), undertake appropriate gastrointestinal tract decontamination procedures, initiate supportive care, administer antidote as needed (see manufacturer's product monograph), consult with a Regional Poison Control Centre regarding ongoing management, and arrange for appropriate follow-up care.

PHARMACEUTICAL INFORMATION

The components of pms-ACETAMINOPHEN WITH CODEINE ELIXIR (acetaminophen and codeine phosphate) have the following structural formulae:

Acetaminophen

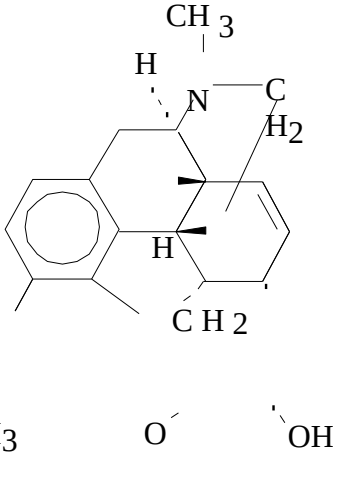


Chemical Name: N-(4-hydroxyphenyl) acetamide

Molecular Formula: $C_8H_9NO_2$

Molecular Weight: 151.2 g/Mol

Codeine Phosphate



•H_3PO_4 •½H_2O

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

Molecular Formula: $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$

Molecular Weight: 406.4 g/Mol

Physical Properties:

Acetaminophen	-	white crystalline powder
Codeine phosphate	-	white crystalline powder

Solubility:

Acetaminophen	-	in boiling water 1 g/20 mL; in alcohol 1 g/10 mL
Codeine phosphate	-	in water 4 g/mL; in alcohol 30 mg/10 mL

Stability and Storage Recommendations:
Store between 15°C and 30°C in tight, light-resistant containers.

AVAILABILITY OF DOSAGE FORMS

pms-ACETAMINOPHEN WITH CODEINE ELIXIR:
Each 5 mL of elixir contains: acetaminophen 160 mg and codeine phosphate 8 mg in a clear red liquid. Non-medicinal ingredients: Alcohol, Artificial Butterscotch Flavour, Artificial Cherry Flavour, Caramel Colour, Citric Acid (for pH adjustment), FD & C Red No.40, Glycerin, Methylparaben, Propylparaben, Purified Water, Natural Orange Extract, Propylene Glycol, Sodium Citrate (for pH adjustment), Sodium Saccharin, Sucrose.

Available in bottle of 100 mL and 500 mL.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

N pms-ACETAMINOPHEN WITH CODEINE ELIXIR

Read this carefully before you start taking pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR.

Serious Warnings and Precautions

- **Even if you take pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR. 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR. They could die from taking it. If a person has not been prescribed pms-ACETAMINOPHEN WITH CODEINE ELIXIR, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR used for?

Pain: pms-ACETAMINOPHEN WITH CODEINE ELIXIR is used for adults for short-term relief of mild to moderate pain of various causes.

pms-ACETAMINOPHEN WITH CODEINE ELIXIR should not be taken for pain for more than 5 days, or fever for more than 3 days, unless directed by your healthcare professional.

How does pms-ACETAMINOPHEN WITH CODEINE ELIXIR work?

Codeine: Codeine belongs to a class of drugs which is commonly referred to as opiates, opioids or narcotics, and also includes fentanyl, hydromorphone, morphine and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

Acetaminophen: Acetaminophen belongs to a group of medicines called analgesics (pain relievers) and antipyretics (fever reducers). The exact mechanism of action of acetaminophen is not known.

What are the ingredients in pms-ACETAMINOPHEN WITH CODEINE ELIXIR?

Medicinal ingredients: Acetaminophen and Codeine phosphate

Non-medicinal ingredients: Alcohol, Artificial Butterscotch Flavour, Artificial Cherry Flavour, Caramel Colour, Citric Acid (for pH adjustment), FD & C Red No.40, Glycerin, Methylparaben, Propylparaben, Purified Water, Natural Orange Extract, Propylene Glycol, Sodium Citrate (for pH adjustment), Sodium Saccharin, Sucrose.

pms-ACETAMINOPHEN WITH CODEINE ELIXIR comes in the following dosage forms:
Oral solution: 160 mg / 8 mg per 5 mL

Do not use pms-ACETAMINOPHEN WITH CODEINE ELIXIR if:

- your doctor did not prescribe it for you
- your pain is mild
- you are allergic to acetaminophen or codeine phosphate or any of the other ingredients in pms-ACETAMINOPHEN WITH CODEINE ELIXIR
- 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 slow or shallow breathing, elevated carbon dioxide levels in the blood or a condition called “cor pulmonale” in which part of the heart is enlarged or does not work correctly due to high blood pressure in the lungs
- you have any heart problems

- 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 having seizures
- you suffer from alcoholism
- you have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen, or are at risk of blocked intestines;
- you had surgery less than 24 hours ago;
- 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
- have been told by your doctor that you break down codeine rapidly. This can lead to codeine overdose even at the usual adult dose
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding. The use of codeine-containing products while breast-feeding may harm your baby. If you breastfeed and take pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR
- you are less than 12 years old
- 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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-ACETAMINOPHEN WITH CODEINE ELIXIR. 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), 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
- are under a physician's care

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, especially in patients younger than 18 years of age. Stop taking pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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.

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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR if you are under 18 years of age and you are at risk for a breathing problem because you:

- have obstructive sleep apnea
- are obese
- have an existing lung problem

Sleep apnea: Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your doctor if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

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

If you are pregnant and are taking pms-ACETAMINOPHEN WITH CODEINE ELIXIR, 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR. 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR. pms-ACETAMINOPHEN WITH CODEINE ELIXIR can cause:

- drowsiness
- dizziness or
- lightheadedness

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

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 pms-ACETAMINOPHEN WITH CODEINE 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.).

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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR.

Serotonin Syndrome:
pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR with certain anti-depressants, muscle relaxants 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking pms-ACETAMINOPHEN WITH CODEINE ELIXIR. 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR
- 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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
- drugs used to treat migraines (e.g. triptans)
- 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
- St. John's Wort

How to take pms-ACETAMINOPHEN WITH CODEINE ELIXIR:

- Your doctor will prescribe the lowest dose that works to control your pain symptoms.
- It is recommended that you only take pms-ACETAMINOPHEN WITH CODEINE ELIXIR for up to 3 days for fever, and up to 5 days for pain. If you need to take pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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.

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.

Review your pain regularly with your doctor to determine if you still need pms-ACETAMINOPHEN WITH CODEINE ELIXIR. Be sure to use pms-ACETAMINOPHEN WITH CODEINE ELIXIR only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking pms-ACETAMINOPHEN WITH CODEINE ELIXIR, tell your doctor immediately.

Usual dose (Adults):

Adults: 10 mL to 20 mL every 4 hours as required if necessary. Do not take more than 5 doses in a 24-hour period.

Your doctor should prescribe pms-ACETAMINOPHEN WITH CODEINE ELIXIR at the lowest effective dose for the shortest period of time. Take pms-ACETAMINOPHEN WITH CODEINE ELIXIR every 4-6 hours as needed

Stopping your Medication

If you have been taking pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR. 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 pms-ACETAMINOPHEN

WITH CODEINE ELIXIR.

Refilling your Prescription for pms-ACETAMINOPHEN WITH CODEINE ELIXIR:
A new written prescription is required from your doctor each time you need more pms-ACETAMINOPHEN WITH CODEINE ELIXIR. 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 illness.

Overdose:

Overdose may result in **severe or possibly fatal liver damage.**

If you think you have taken too much pms-ACETAMINOPHEN WITH CODEINE ELIXIR., 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR?

These are not all the possible side effects you may feel when taking pms-ACETAMINOPHEN WITH CODEINE ELIXIR. 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR.

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 toxicity: a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid			✓

muscles			
Serious Skin Reactions (Stevens - Johnson Syndrome, Toxic Epidermal Necrolysis, Hypersensitivity Syndrome): any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or joint pain, yellowing of the skin or eyes, dark urine.			✓
VERY RARE			
Liver Injury: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		✓	
Redness or swelling in the area of pain, symptoms that do not improve, or if new symptoms appear such as fever, rash, itching, wheezing or persistent headache.		✓	

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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR, get emergency help right away.

- **Store between 15°C and 30°C in tight, light-resistant containers.**

Disposal:
pms-ACETAMINOPHEN WITH CODEINE ELIXIR 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 pms-ACETAMINOPHEN WITH CODEINE ELIXIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Heath Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website www.pharmascience.com, or by calling 1-888-550-6060.

This leaflet was prepared by:

Pharmascience Inc.
Montréal, Québec
H4P 2T4
www.pharmascience.com

Last revised: July 28, 2020