PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N] ATASOL-15

Acetaminophen, Caffeine Citrate, Codeine Phosphate

Tablet (325 mg, 30 mg, 15 mg)

[N] ATASOL-30

Acetaminophen, Caffeine Citrate, Codeine Phosphate

Tablet (325 mg, 30 mg, 30 mg)

Analgesic - Antipyretic

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ATASOL-15 & ATASOL-30

Acetaminophen, Caffeine Citrate, Codeine Phosphate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Product	Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Atasol-15	Oral	Tablet / Acetaminophen 325 mg Caffeine Citrate 30 mg Codeine Phosphate 15 mg	Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Crospovidone, D&C Yellow 10 Aluminum Lake, FD&C Yellow 6 Aluminum Lake, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Stearic Acid, Water.
Atasol-30	Oral	Tablet / Acetaminophen 325 mg Caffeine Citrate 30 mg Codeine Phosphate 30 mg	Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Crospovidone, D&C Yellow 10 Aluminum Lake, FD&C Blue 1 Aluminum Lake, FD&C Red 40 Aluminum Lake, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Stearic Acid, Water.

INDICATIONS AND CLINICAL USE

Adults

ATASOL-15 & ATASOL-30 is indicated for the relief of mild to moderate pain associated with conditions such as headache, dental pain, muscle pain, rheumatic pain, menstrual pain and the discomfort of fevers due to colds and/or flu.

ATASOL-15 & ATASOL-30 is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age)

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

Pediatrics (< 18 years of age)

The safety and efficacy of ATASOL-15 & ATASOL-30 has not been studied in the pediatric population. The use of ATASOL-15 & ATASOL-30 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: Regardless of clinical setting, codeine (including ATASOL-15 & ATASOL-30) 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 **CONTRAINDICATIONS**; also **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substances acetaminophen, caffeine citrate, and codeine phosphate or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients known to be CYP2D6 ultra-rapid metabolizers for whom there is an increased risk of developing symptoms of opioid toxicity, even at commonly prescribed doses (see **WARNINGS AND PRECAUTIONS**)
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome
- Pediatric patients less than 12 years of age
- Women who are breast-feeding, and during pregnancy, or during labour and delivery (**see Serious Warnings and Precautions, and Warnings and Precautions**).

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, ATASOL-15 & ATASOL-30 (acetaminophen, caffeine citrate 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

ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 or following a dose increase.

Tablets: ATASOL-15 & ATASOL-30 must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 especially by children, can result in a fatal overdose of acetaminophen, caffeine citrate and, codeine phosphate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of ATASOL-15 & ATASOL-30 during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

SERIOUS WARNINGS AND PRECAUTIONS

Interaction with Alcohol

The co-ingestion of alcohol with ATASOL-15 & ATASOL-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) depressant, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 (acetaminophen, caffeine citrate, 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. ATASOL-15 & ATASOL-30 should be stored securely to avoid theft or misuse.

ATASOL-15 & ATASOL-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 **ATASOL-15 & ATASOL-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 codeine phosphate can occur at particularly high doses. A codeine phosphate dose reduction or change in opioid may be required.

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

Abuse and Misuse

Like all opioids, **ATASOL-15 & ATASOL-30** is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, **ATASOL-15 & ATASOL-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 **ATASOL-15 & ATASOL-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.

ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30.

The use of **ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-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).**

Endocrine

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

Use in Drug and Alcohol Addiction

ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30; extreme caution and awareness is warranted to mitigate the risk.

Gastrointestinal Effects

Codeine phosphate and other morphine-like opioids have been shown to decrease bowel motility. Codeine 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 ATASOL-15 & ATASOL-30 is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic

Serotonin Syndrome: ATASOL-15 & ATASOL-30 could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, 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. ATASOL-15 &

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when ATASOL-15 & ATASOL-30 is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advice 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**).

ATASOL-15 & ATASOL-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 acetaminophen, caffeine citrate, and 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, acetaminophen, caffeine citrate, and codeine phosphate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, codeine phosphate must be used with extreme caution and only if it is judged essential

(see **CONTRAINDICATIONS).**

Risk of Death in Ultra-Rapid Metabolizers of Codeine

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labelled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. (See also Labour, Delivery and Nursing Women in **Special Populations**).

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

ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 for at least 24 hours before the operation and ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-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, caffeine citrate, 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.

ATASOL-15 & ATASOL-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
ATASOL-15 & ATASOL-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, caffeine citrate 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. Acetaminophen, caffeine citrate, and 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 ATASOL-15 & ATASOL-30 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 ATASOL-15 & ATASOL-30 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 ATASOL-15 & ATASOL-30 are essential. Overestimating the ATASOL-15 & ATASOL-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**).

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

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

- Avoid the use of codeine-containing products in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with ATASOL-15 & ATASOL-30 as in these patients, even usual therapeutic doses of ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes
The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ATASOL-15 & ATASOL-30 requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. (See **Drug Interactions,** Interactions with Drugs Affecting Cytochrome P450 Isoenzymes).

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**).

Special Populations
Special Risk Groups: Acetaminophen, caffeine citrate, 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, glaucoma, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in humans have not been conducted. ATASOL-15 & ATASOL-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, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS),).**

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, ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 is used in this population.

Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. **However, some women are ultra-rapid metabolisers of codeine (**see **CONTRAINDICATIONS, Ultra-Rapid Metabolisers of Codeine; and WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-rapid Metabolizers of Codeine). These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breast-fed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death in nursing infants.**

Since there is a risk of infant exposure to codeine and morphine through breast milk, ATASOL-15 and ATASOL-30 are contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breast-feeding.

Pediatrics (< 18 years of age):
The safety and efficacy of ATASOL-15 & ATASOL-30 has not been studied in the pediatric population. The use of ATASOL-15 & ATASOL-30 is not recommended in between 12 and 18 years of age and is contraindicated in those under 12.

Contraindicated in < 12 years of age:
Regardless of clinical setting, codeine (including ATASOL-15 and ATASOL-20) 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 **WARNINGS AND PRECAUTIONS**, **Special Populations, Pediatrics**; also **DOSAGE AND ADMINISTRATION**).

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

Patients with Hepatic Impairment:
Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatoxicity 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** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**, **Hepatic Impairment**).

Patients with Renal Impairment:
ATASOL-15 & ATASOL-30 should be given with caution in patients with severe impairment of renal function (see **DOSAGE AND ADMINISTRATION).**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of ATASOL-15 & ATASOL-30 (acetaminophen, caffeine citrate, 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 ATASOL-15 & ATASOL-30 are drowsiness, light-headedness, 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, pruritis, rash, thrombocytopenia, and agranculocytosis.

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

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 physiological 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

This drug may enhance the effects of other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlorodiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS**, **Neurologic**, **Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). ATASOL-15 & ATASOL-30 should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

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

Drug-Drug Interactions

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

Cimetidine:
Concurrent administration of cimetidine with opioids may lead to increased effect or toxicity of opioid analgesics.

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.

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

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 ATASOL-15 & ATASOL-30 while taking CYP3A4 inducers, CYP3A4 inhibitors, or CYP2D6 inhibitors. If concomitant use is necessary, monitor patients for respiratory depression and sedation at frequent intervals or for signs of opioid withdrawal.

CYP3A4 inhibitors: The concomitant use of ATASOL-15 & ATASOL-30 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 ATASOL-15 & ATASOL-30.

CYP2D6 inhibitors: The concomitant use of ATASOL-15 & ATASOL-30 and CYP2D6 inhibitors (e.g., amiodarone, quinidine) may result in a decrease in active metabolite morphine plasma concentration, leading to decreased efficacy or symptoms of opioid withdrawal. The discontinuation of a concomitantly used CYP2D6 inhibitor may lead to an increased metabolism to morphine, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

CYP3A4 inducers: The concomitant use of ATASOL-15 & ATASOL-30 and CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, may result in a decreased plasma concentration of codeine and its active metabolite morphine, leading to decreased efficacy or symptoms of opioid withdrawal. The discontinuation of a concomitantly used CYP3A4 inducer can increase the plasma concentration of codeine and its active metabolite morphine which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

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

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

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

DOSAGE AND ADMINISTRATION

ATASOL-15 & ATASOL-30 should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

ATASOL-15 & ATASOL-30 must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving ATASOL-15 & ATASOL-30 can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Contraindication in Children under 12
Regardless of clinical setting, codeine (including **ATASOL-15 & ATASOL-30)** 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 ATASOL-15 & ATASOL-30 be used for a maximum of 7 days at the lowest dose that provides adequate pain 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 ATASOL-15 & ATASOL-30 is 4 tablets, which is 60 and 120 mg codeine, respectively (9 and 18 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 (see **D&A - Adjustment or reduction of Dosage**).

Dosing Considerations
ATASOL-15 & ATASOL-30 (acetaminophen, caffeine citrate, 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**).

ATASOL-15 & ATASOL-30 is not indicated for rectal administration.

ATASOL-15 & ATASOL-30 may be taken with or without food, with a glass of water.

Recommended Dose and Dosage Adjustment

Adults:
Take 1-2 tablets every 4 to 6 hours as needed, up to a maximum of 4 tablets daily or as recommended by a physician or a dentist.

Codeine, including ATASOL-15 & ATASOL-30, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 4-6 hours and not on scheduled intervals.

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. 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**).

Patients with Renal Impairment: In patients with severe impairment of renal function, the dose initiation should follow a conservative approach. Atasol-15 & Atasol-30 should be initiated at a low dose (see **DOSAGE AND ADMINISTRATION**).

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. ATASOL-15 & ATASOL-30 should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

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 **ATASOL-15 &ATASOL-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.

Disposal

ATASOL-15 &ATASOL-30 should be kept in a safe place, out of the sight and reach of children before, during and after use. ATASOL-15 &ATASOL-30 should not be used in front of children, since they may copy these actions.

ATASOL-15 &ATASOL-30 should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired ATASOL-15 &ATASOL-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: 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.

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: Narcotic/Opiate

Treatment:
Specific Antidote: Naloxone HCl.

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

Caffeine:
Symptoms: Xanthine (theophylline-like picture), CNS excitation, skeletal muscle irritability

Treatment:
Specific Antidote: None.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
ATASOL-15 & ATASOL-30 (acetaminophen, caffeine citrate, and codeine phosphate) combine

the analgesic effects of the centrally acting analgesic codeine, with a peripherally acting analgesic, acetaminophen. Caffeine stimulates the CNS at all levels including the cerebral cortex. In addition, it acts on the kidney to produce mild diuresis, stimulates cardiac muscle, and depresses smooth muscle.

Acetaminophen, caffeine citrate, 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 liver accounts for 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.

Caffeine is absorbed efficiently from the gastrointestinal tract, and peak plasma concentrations Occur 15 to 120 minutes after ingestion. It is almost completely metabolized via oxidation, demethylation, and acetylation, with only about 1% of caffeine excreted via the urine. The principal metabolites in man are methyluric acid, 1-methylxanthine, paraxanthine, and theobromine.

Pharmacodynamics

Following oral administration of acetaminophen in combination with codeine, both drugs are rapidly absorbed with peak plasma levels occurring within 60 minutes.

Following oral administration, caffeine is rapidly absorbed with a peak plasma level occurring within 15 to 120 minutes. Given an oral dose of 100 mg peak plasma caffeine concentrations of 1.5 to 1.8 μg/ml are reached within 60 minutes.

The plasma elimination half-life (t1/2) ranges from 1.5 to 3.5 hours for acetaminophen, 1.5 to 4 hours for codeine and from 2.5 to 4.5 hours for caffeine. 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 or caffeine, and less than 4% of an administered dose of acetaminophen, is excreted unchanged in the urine.

Central Nervous System:

Codeine phosphate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

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

Codeine phosphate causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of codeine phosphate overdose.

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

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

Endocrine System:
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

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

Hepatic Impairment: Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatoxicity 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**).

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**).

STORAGE AND STABILITY
ATASOL-15 & ATASOL-30 should be stored at controlled room temperature (15°C – 25°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

ATASOL-15 tablets

Composition:
Actives ingredients: Acetaminophen 325 mg, caffeine citrate 30 mg, codeine phosphate 15 mg

Non-medicinal ingredients**:** Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Crospovidone, D&C Yellow 10 Aluminum Lake, FD&C Yellow 6 Aluminum Lake, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Stearic Acid, Water.

Packaging:
Bottle 100 tablets

ATASOL-30 tablets

Composition:
Actives ingredients: Acetaminophen 325 mg, caffeine citrate 30 mg, codeine phosphate 30 mg

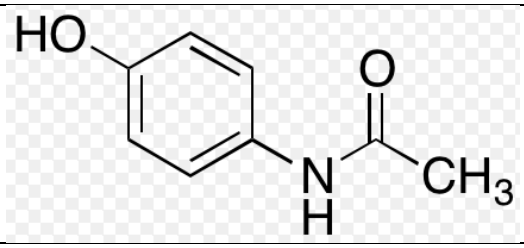
Non-medicinal ingredients**:** Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Crospovidone, D&C Yellow 10 Aluminum Lake, FD&C Blue 1 Aluminum Lake, FD&C Red 40 Aluminum Lake, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Stearic Acid, Water.

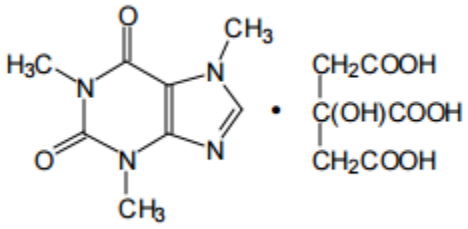
Packaging:
Bottle 100 tablets

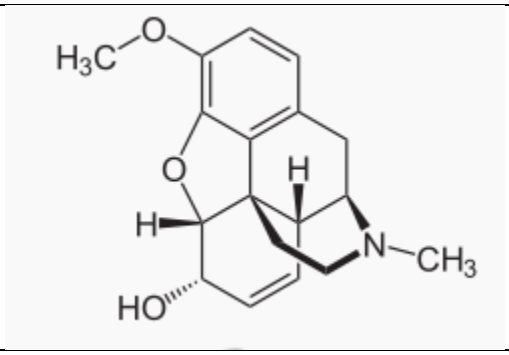
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Acetaminophen
Chemical Name:	Acetamide, *N*-(4-hydroxyphenyl)-; 4'-Hydroxyacetanilide
Other Names:	Paracetamol
Chemical Structure:	
	
Molecular Formula:	$C_8H_9NO_2$
Molecular Weight:	151.16
Physical Form:	White crystalline powder
Solubility:	12.78 mg/mL(in water at 20°C)
Density:	1.293 g/cm^3
Melting Point Range:	168°C - 172°C

Proper Name:	Caffeine Citrate
Chemical Name:	1,3,7-trimethylpurine-2,6-dione 2-hydroxypropane-1,2,3-tricarboxylic acid
Other Names:	N/A
Chemical Structure:	
	
Molecular Formula:	$C_{14}H_{18}N_4O_9$
Molecular Weight:	386.314
Physical Form:	White Powder
Solubility:	Soluble in water
pH:	Neutral
Melting Point Range:	235.6°C – 236.2°C

Proper Name:	Codeine phosphate
Chemical Name:	Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5 α,6 α)-, phosphate (1:1) (salt), hemihydrate 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol, phosphate (1:1) (salt) hemihydrate
Other Names:	N/A
Chemical Structure:	
	
Molecular Formula:	$C_{18}H_{21}NO_3.H_3PO_4.$ ½ H_2O
Molecular Weight:	406.37
Physical Form:	White powder
Solubility:	Soluble in cold water, Partially soluble in methanol. Insoluble in diethyl ether.

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

ATASOL-15 & ATASOL-30
Acetaminophen, caffeine citrate, and codeine phosphate tablets

Read this carefully before you start taking **ATASOL-15 & ATASOL-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 **ATASOL-15 & ATASOL-30.**

Serious Warnings and Precautions

- **Even if you take ATASOL-15 & ATASOL-30 as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take ATASOL-15 & ATASOL-30 it must be swallowed whole. Do not cut, break, crush, chew, dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30. They could die from taking it. If a person has not been prescribed ATASOL-15 & ATASOL-30, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 used for?

ATASOL-15 & ATASOL-30 is used in adults for the relief of mild to moderate pain associated with conditions such as headache, dental pain, muscle pain, rheumatic pain, menstrual pain and the discomfort of fevers due to colds and/or flu.

How does ATASOL-15 & ATASOL-30 work?

ATASOL-15 and ATASOL-30 consist of codeine, acetaminophen, and caffeine.

Codeine 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.

Acetaminophen reduces pain and fever. Caffeine is a mild stimulant which may enhance pain-relieving effects.

What are the ingredients in ATASOL-15 & ATASOL-30?

ATASOL-15
Medicinal ingredients: Acetaminophen 325 mg, caffeine citrate 30 mg, codeine phosphate 30 mg
Non-medicinal ingredients: Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Crospovidone, D&C Yellow 10 Aluminum Lake, FD&C Yellow 6 Aluminum Lake, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Stearic Acid, Water.

ATASOL-30
Medicinal ingredients: Acetaminophen 325 mg, caffeine citrate 30 mg, codeine phosphate 30 mg
Non-medicinal ingredients: Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Crospovidone, D&C Yellow 10 Aluminum Lake, FD&C Blue 1 Aluminum Lake, FD&C Red 40 Aluminum Lake, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Stearic Acid, Water.

ATASOL-15 & ATASOL-30 comes in the following dosage forms:

ATASOL-15
Bottle 100 tablets

ATASOL-30
Bottle 100 tablets

Do not use ATASOL-15 & ATASOL-30 if:

- Your doctor did not prescribe it for you
- you are allergic to acetaminophen, caffeine citrate, and codeine phosphate or any of the other ingredients in **ATASOL-15 & ATASOL-30** (see **What are the ingredients in ATASOL-15 & ATASOL-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 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 have a brain tumor
- you suffer from alcoholism
- 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 ATASOL-15 & ATASOL-30, 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 ATASOL-15 & ATASOL-30.
- 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.you have suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- You have acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- You have severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ATASOL-15 & ATASOL-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 low blood pressure
- have past or current depression

- suffer from chronic or severe constipation
- have problems with your adrenal or prostate gland
- have persistent or chronic cough (as occurs with smoking), glaucoma, high blood pressure
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past, hallucinations or other severe mental problems
- are planning to become pregnant
- suffer from migraines

Other warnings you should know about:

Some people metabolize codeine at a much faster rate than the general population. This may lead to accidental overdose. Stop taking ATASOL-15 & ATASOL-30 and seek immediate medical helps 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 ATASOL -15 & ATASOL 30 if you are under 18 years of age and you are at risk for breathing problems because you:
  - have obstructive sleep apnea
  - are obese
  - have an existing lung problem

Pregnancy, nursing, labour and delivery: Do not use ATASOL-15 & ATASOL-30 while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. ATASOL-15 & ATASOL-30 can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking ATASOL-15 & ATASOL-30, 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 ATASOL-15 & ATASOL-30. 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 ATASOL-15 & ATASOL-30. ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30.

Serotonin Syndrome: ATASOL-15 & ATASOL-30can 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 ATASOL-15 & ATASOL-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.

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 ATASOL-15 & ATASOL-30:

- alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-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 **ATASOL-15 & ATASOL-30** 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
- some anti-retroviral drugs (used to treat viral infections)
- some anti-fungal drugs (used to treat fungal infections)
- some antibiotic drugs (used to treat bacterial infections)
- some heart medication (such as beta blockers)
- tranquilizers, sedatives, sedating antihistamines, other depressants
- grapefruit juice
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take ATASOL-15 & ATASOL-30:

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:

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 ATASOL-15 & ATASOL-30 for up to 7 days. If you need to take ATASOL-15 & ATASOL-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.

Take 1-2 tablets every 4 to 6 hours as needed, up to a maximum of 4 tablets daily or as recommended by a physician or a dentist.

Review your pain regularly with your doctor to determine if you still need ATASOL-15 & ATASOL-30. Be sure to use ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30, tell your doctor immediately.

Stopping your Medication

If you have been taking ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30. 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 ATASOL-15 & ATASOL-30.

Refilling your Prescription for ATASOL-15 & ATASOL-30:

A new written prescription is required from your doctor each time you need more **ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30?

These are not all the possible side effects you may feel when taking ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30 in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30, get emergency help right away.**
- **Store tablets at room temperature (15˚- 25˚C). Keep in a dry place.**

Disposal:

ATASOL-15 & ATASOL-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 ATASOL-15 & ATASOL-30:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.atasol.ca or by calling 1-800-268-3186.

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