PRESCRIBING INFORMATION

INCLUDING PATIENT MEDICATION INFORMATION

[N]TEVA-LENOLTEC No. 1

Acetaminophen, Caffeine and Codeine Phosphate Tablets

300 mg / 15 mg / 8 mg

Teva Standard

Tablets and Caplets

Analgesic - Antipyretic

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TABLE OF CONTENTS

NTEVA-LENOLTEC No. 1

Acetaminophen, Caffeine and Codeine Phosphate Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	300 mg acetaminophen, 15 mg caffeine and 8 mg codeine phosphate	Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Silica Colloidal anhydrous

INDICATIONS AND CLINICAL USE

Adults

TEVA-LENOLTEC No.1 (acetaminophen, caffeine and codeine phosphate) is indicated for the short-term relief of mild to moderate pain.

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.

Pediatrics (< 18 years of age)

There are limited safety and efficacy studies with acetaminophen and codeine in the pediatric population. Therefore, the use of TEVA-LENOLTEC No. 1 is not recommended in patients over 12 and under 18 years of age.

Regardless of clinical setting, the use of codeine, including TEVA-LENOLTEC No. 1, is contraindicated in patients below the age of 18 years due to increased safety concerns (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).**

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance acetaminophen, caffeine 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.

- 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 with severe hepatic or renal impairment (see **WARNINGS AND PRECAUTIONS, Special Populations**, **Hepatic Impairment and Renal Impairment**).
- 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, Codeine**).
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are nursing or during labour and delivery (see **SERIOUS WARNINGS AND PRECAUTIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, Labour, Delivery and Nursing Women**).
- Children less than 18 years old.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, TEVA-LENOLTEC No. 1 (acetaminophen, caffeine 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

TEVA-LENOLTEC No. 1 poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1. Infants exposed *in-utero* or through breast milk are at risk of life-threatening respiratory depression upon delivery or when being nursed. Patients should be monitored for respiratory depression, especially during initiation of TEVA-LENOLTEC No. 1 or following a dose increase.

TEVA-LENOLTEC No. 1 must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1, especially by children, can result in a fatal overdose of acetaminophen and codeine phosphate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1 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 usage of TEVA-LENOLTEC No. 1 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
TEVA-LENOLTEC No. 1 should be stored securely to avoid theft or misuse.

Patients should be cautioned not to consume alcohol while taking TEVA-LENOLTEC No. 1 as it may increase the chance of experiencing serious adverse events, including death.

Patients on any opioid for pain should be counselled to consult a physician before using this product.

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. Do not take continuously without medical review.
Patients should be counselled to contact a physician if pain or fever persists or gets worse, or if new symptoms occur.

Patients should be counselled not to use with other products containing acetaminophen, an opioid, or codeine.

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 extreme sleepiness, confusion or shallow breathing, which may be life threatening.

Abuse and Misuse

Like all opioids, TEVA-LENOLTEC No. 1 are a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, TEVA-LENOLTEC No. 1 should be used and handled with caution.

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

Opioids, such as codeine, 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.

TEVA-LENOLTEC No. 1 are intended for oral use only. The tablets should be swallowed whole. 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 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 TEVA-LENOLTEC No. 1.

The use of TEVA-LENOLTEC No. 1 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, psychological and/or physical dependence, and addiction may develop upon repeated administration and/or high doses of TEVA-LENOLTEC No. 1.

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

TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1 unless used under extreme caution and awareness.

Endocrine

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal

function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal Effects

Codeine 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)

Use of TEVA-LENOLTEC No. 1 is not recommended to be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the risks. If TEVA-LENOLTEC No. 1 was used during pregnancy, special attention to NOWS is warranted.

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.

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.

Neurologic

Serotonin toxicity / Serotonin Syndrome: Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with codeine, 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

TEVA-LENOLTEC No. 1 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.

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Codeine 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 TEVA-LENOLTEC No. 1 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**).

TEVA-LENOLTEC No. 1 should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation**, and **DRUG INTERACTIONS**).

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

Head Injury: The respiratory depressant effects of codeine, 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 may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury.

In such patients, codeine must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS).**

Opioid induced hyperalgesia: Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra-operative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful) stimuli (allodynia), in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

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.

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

TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1 for at least 24 hours before the operation and TEVA-LENOLTEC No. 1 should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if TEVA-LENOLTEC No. 1 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 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.

TEVA-LENOLTEC No. 1 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

TEVA-LENOLTEC No. 1 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 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 should be used with extreme caution in patients with compromised respiratory function, such as 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 TEVA-LENOLTEC No. 1, 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 TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1 is essential. Overestimating the TEVA-LENOLTEC No. 1 dose when converting patients from another opioid product can result in a fatal overdose with the first

dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**).

Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. TEVA-LENOLTEC No. 1 is contraindicated in children less than 18 years old. As well, codeine is contraindicated in CYP2D6 ultra-rapid metabolizers (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.

Use in Patients with Chronic Pulmonary Disease: Monitor patients having compromised respiratory function (such as bronchial asthma, pulmonary edema, obstructive airways disease, obesity, obstructive sleep apnea, hypoxia, hypercapnia, or preexisting respiratory depression) for respiratory depression, particularly when initiating therapy and titrating with TEVA-LENOLTEC No. 1, as in these patients, even usual therapeutic doses of TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1 is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

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.

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: Codeine 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. TEVA-LENOLTEC No. 1 crosses the placental barrier and should not be administered to pregnant women unless, in the judgment of the physician, potential benefits outweigh the risks.

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 complications. 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, TEVA-LENOLTEC No. 1 is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression may 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 TEVA-LENOLTEC No. 1 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. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare. However, **some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk**

and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can lead to serious adverse reactions, including death, in nursing infants (see **WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-Rapid Metabolizers of Codeine**).
Caffeine is distributed into the milk of nursing women.

Pediatrics (< 18 years of age): There are limited safety and efficacy studies with acetaminophen and codeine in the pediatric population. Therefore, use of TEVA-LENOLTEC No. 1 is not recommended in patients over 12 and under 18 years of age. TEVA-LENOLTEC No. 1 contains codeine and is contraindicated in children under 18 years of age (see **CONTRAINDICATIONS**).

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**).

Patients with Hepatic Impairment:
Acetaminophen
TEVA-LENOLTEC No. 1 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**).

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:
TEVA-LENOLTEC No. 1 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of TEVA-LENOLTEC No. 1 (acetaminophen, caffeine and codeine phosphate) tablets are similar to those of other opioid analgesics and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed adverse effects of acetaminophen, caffeine and codeine phosphate tablets 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, pruritus, rash, thrombocytopenia, dry mouth, hyperhidrosis, somnolence 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 acetylsalicylic acid (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.

Higher doses of caffeine lead to overstimulation of the higher centres of the CNS. Adverse CNS effects may include insomnia, restlessness, nervousness and mild delirium. Adverse gastrointestinal effects of caffeine may include nausea, vomiting, and gastric irritation. Although chronic administration of caffeine in animals has been associated with gastric ulceration, such a causal relationship in humans has not been adequately established to date.

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.

Cardiac Disorders: (very rare) palpitations, tachycardia
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, insomnia, 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, rash pruritus, urticaria

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. Advise patient to seek medical attention if they experience any of these symptoms.

DRUG INTERACTIONS

Drug-Drug Interactions

Interaction with Benzodiazepines and 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)**. TEVA-LENOLTEC No. 1 should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drugs Associated with a Risk of Serotonin Syndrome:
Coadministration of codeine with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and monoamine oxidase (MAO) inhibitors (used to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), may result in serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

CYP2D6 inhibitors: Codeine analgesia is believed to be dependent upon the cytochrome P450 isoenzyme CYP2D6 catalyzed o-demethylation to form the active metabolite morphine although other mechanisms have been cited. An interaction with quinidine, methadone, and paroxetine (CYP2D6 inhibitors) leading to decreased plasma concentrations of morphine has been described, which may have the potential to decrease codeine analgesia.

Lithium: Acute, single dose, caffeine consumption has been shown to increase renal lithium excretion, which is likely secondary to the increased sodium excretion seen with caffeine use. Additionally, abrupt discontinuation of chronic caffeine use has been associated with

increased serum lithium concentrations.

Warfarin-like compounds: 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.

Flucloxacillin: High anion gap metabolic acidosis from pyroglutamic acid (5-oxoprolinemia) has been reported with concomitant use of therapeutic doses of paracetamol and flucloxacillin. Patients reported to be most at risk are elderly females with underlying disease such as sepsis, renal function abnormality, and malnutrition. Most patients improve after stopping one or both of the drugs. Patients should be instructed to ask their health care provider before use if they are taking the antibiotic flucloxacillin.

Drug-Laboratory Interactions

Codeine may increase serum amylase levels.

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

Drug-Lifestyle Interactions

Limit use of other caffeine-containing medications, food and beverages. The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

TEVA-LENOLTEC No. 1 should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

TEVA-LENOLTEC No. 1 must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving TEVA-LENOLTEC No. 1 can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

For acute pain, it is recommended that TEVA-LENOLTEC No. 1 be used for a maximum of 5 days at the lowest dose that provides adequate pain relief. For fever, it is recommended that TEVA-LENOLTEC No. 1 be used for a maximum of 3 days at the lowest dose that provides adequate fever relief.

Dosing Considerations

TEVA-LENOLTEC No. 1 (acetaminophen, caffeine 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**).

TEVA-LENOLTEC No. 1 is not indicated for rectal administration.

TEVA-LENOLTEC No. 1 may be taken with or without food with a glass of water.

TEVA-LENOLTEC No. 1 is contraindicated in children less than 18 years old (see **CONTRAINDICATIONS**).

Codeine, including TEVA-LENOLTEC No. 1, should be used 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 TEVA-LENOLTEC No. 1 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.

TEVA-LENOLTEC No. 1 tablets and caplets are given orally.

DOSAGE:

TEVA-LENOLTEC No. 1:
Adults (> 18 years of age):
Take 1 caplet/tablet every 4-6 hours, not to exceed 12 caplets/tablets in 24 hours. If pain does not respond to 1 caplet/tablet, take 2 caplets/tablets at next dose.

Based on the dosage guidance, the number of tablets per dose, and the maximum number of tablets per 24 hours, should be conveyed in the prescription.

Disposal

TEVA-LENOLTEC No. 1 should be kept in a safe place, out of the sight and reach of children before, during and after use. TEVA-LENOLTEC No. 1 should not be used in front of children, since they may copy these actions.

TEVA-LENOLTEC No. 1 should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired TEVA-LENOLTEC No. 1 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:

Hepatobiliary Disorders: If an acetaminophen extended release product is involved or if the exact formulation is not known, it is recommended to obtain an additional plasma acetaminophen level 4 to 6 hours following the initial acetaminophen level as these levels will continue to rise with the extended release products and may alter treatment decisions.

In adults and adolescents (≥ 12 years of age), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 g over a period of 8 hours or less. Fatalities are infrequent (less than 3 to 4% of untreated cases) and have rarely been reported with overdoses of less than 15 g. In children (< 12 years of age), an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity. Early symptoms following a potentially hepatotoxic overdose may include: anorexia, nausea, vomiting, diaphoresis, pallor and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Serious toxicity or fatalities have been extremely infrequent following an acute acetaminophen overdose in young children, possibly because of differences in the way they metabolize acetaminophen.

Symptoms: Table 1 shows 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.

Typical Toxidrome: 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.

Specific Antidote: NAC (N-acetylcysteine) administered by either the intravenous or the oral route is known to be a 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.

Treatment: When the possibility of acetaminophen overdose exists, treatment should begin immediately and include appropriate decontamination of the gastrointestinal 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 for full recovery.

Codeine:

Symptoms: Risks of codeine overdose include asthenia, cardiorespiratory 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.

Caffeine:
Typical Toxidrome: Xanthine (theophylline-like picture), CNS excitation, skeletal muscle irritability
Specific Antidote: None

Treatment: Stabilize the patient (A, B, Cs), undertake appropriate gastrointestinal tract decontamination procedures, initiate supportive care, consult with a Regional Poison Control Centre regarding ongoing management, and arrange for appropriate follow-up care.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TEVA-LENOLTEC No. 1 (acetaminophen, caffeine and codeine phosphate) combine the analgesic effects of codeine with acetaminophen. Caffeine stimulates the central nervous system (CNS) at all levels including the cerebral cortex. In addition, it acts on the kidneys to produce mild diuresis, stimulates cardiac muscle, and depresses smooth muscle.

Pharmacodynamics

Central Nervous System:
Codeine 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 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 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 overdose.

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

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

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

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

Pharmacokinetics

Absorption:
Acetaminophen, codeine phosphate and caffeine are well absorbed while taken orally.

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 of 300 mg acetaminophen, 15 mg caffeine and 30 mg codeine phosphate, 600 mg acetaminophen produces a peak plasma level of 6.25 mcg/mL within 40 minutes; 60 mg codeine phosphate produces a peak plasma level of 150 ng/mL within 60 minutes.

Caffeine is absorbed efficiently from the gastrointestinal tract, and peak plasma concentrations occur 15 to 120 minutes after ingestion.

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 mcg/mL are reached within 60 minutes.

Distribution:
Acetaminophen is distributed throughout most tissues of the body.

Metabolism:
Acetaminophen is metabolized primarily in the liver.

Metabolism for acetaminophen and codeine is relatively rapid; the principal metabolites are conjugates of glucuronic acid which are excreted in the urine. Metabolism of caffeine is relatively slower and its metabolites are excreted in the urine.

Once absorbed, codeine undergoes complex metabolism through the cytochrome P450 2D6 (CYP2D6) and 3A4 (CYP3A4) isoenzymes. The metabolites undergo further glucuronidation through the uridyl glucuronosyltransferase-2B7 (UGT2B7) isoenzyme to form 3- and 6-glucuronide metabolites which are eliminated through the urine. Approximately 10% of absorbed codeine is metabolized to morphine and morphine-6-glucuronide, which are equipotent and the predominant source of the analgesic effects of codeine.

CYP2D6 and UGT2B7 are known to have genotype polymorphism. For CYP2D6, the genotype polymorphism results in ultra-rapid, extensive, intermediate, and poor metabolizers. For UGT2B7, a single-nucleotide polymorphism in its coding region (UGT2B7*2) increases the activity of the gene product. The increase may be further enhanced in individuals of homozygous UGT2B7*2. It is estimated that homozygous UGT2B7*2 occurs in 25.3% of the Caucasian populations, with a combined CYP2D6 ultra-rapid metabolizer and UGT2B7*2 genotype at 1.4% (range 0.25–2.5%).

Caffeine 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.

Excretion:

The individual plasma elimination half-life ($t_{1/2}$) ranges from 1.5 to 3.5 hours for acetaminophen, 1.5 to 4 hours for codeine, and 2.5 to 4.5 hours for caffeine. 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.

Special Populations and Conditions

Pediatrics: The use of TEVA-LENOLTEC No. 1 is not recommended in patients over 12 and under 18 years of age. TEVA-LENOLTEC No. 1 contains codeine and are contraindicated in children under 18 years of age (see **CONTRAINDICATIONS**).

STORAGE AND STABILITY

TEVA-LENOLTEC No. 1 Tablets: Keep bottle tightly closed. Protect from light. Store between 15ºC - 30ºC.

Do not use if neckband is damaged.

Keep out of the sight and reach of children.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-LENOLTEC No. 1 caplets**:** Each white, oblong, biconvex caplet, imprinted TEC 1 on one side, reverse side plain, contains: acetaminophen 300 mg, caffeine 15 mg and codeine phosphate 8 mg. Also contains as non-medicinal ingredients: Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Silica Colloidal anhydrous. Alcohol-, Sucrose, Tartrazine-, Sulfite-, Paraben- and Gluten-free. Energy: 0.123 kcal. Available in bottles of 30, 100 and 200 caplets.

TEVA-LENOLTEC No. 1 tablets**:** Each round white, biplane tablet, imprinted TEC 1 on one side, reverse side plain, contains: acetaminophen 300 mg, caffeine 15 mg and codeine phosphate 8 mg. Also contains as non-medicinal ingredients: Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Silica Colloidal anhydrous. Paraben and Gluten free. Energy: 0.123 kcal. Available in bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

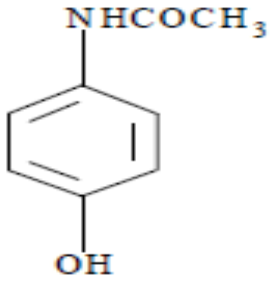
Proper name: **Acetaminophen**

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

Molecular formula: $C_8H_9NO_2$

Molecular weight: 151.2 g/mol

Structural formula:



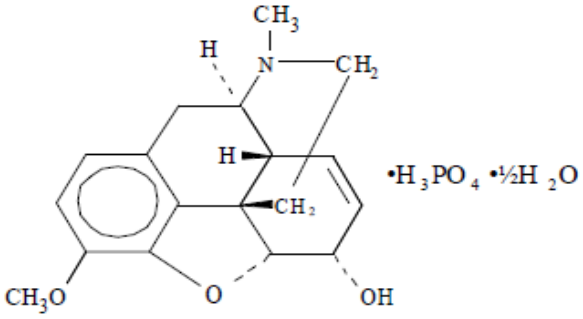
Proper name: **Codeine Phosphate**

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

Molecular formula: $C_{18}H_{21}NO_3 \bullet H_3PO_4 \bullet ½H_2O$

Molecular weight: 406.4 g/mol

Structural formula:



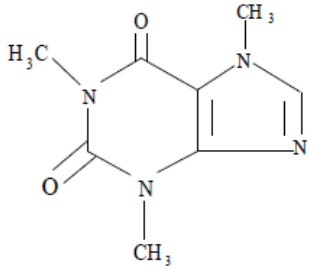
Proper name: **Caffeine**

Chemical name: 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione

Molecular formula: $C_8H_{10}N_4O_2$

Molecular weight: 194.19 g/mol

Structural formula:



REFERENCES

Product Monograph for TYLENOL with Codeine No. 2 and TYLENOL with Codeine No. 3, Control No. 258437, Date of revision December 1, 2021.

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

[N]TEVA-LENOLTEC No. 1
Acetaminophen, Caffeine and Codeine Phosphate Tablets

Read this carefully before you start taking **TEVA-LENOLTEC No. 1** 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 TEVA-LENOLTEC No. 1.

Serious Warnings and Precautions

- **Even if you take TEVA-LENOLTEC No. 1 as directed, you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take TEVA-LENOLTEC No. 1, it must be swallowed whole. Do not cut, break, crush, chew or 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 TEVA-LENOLTEC No. 1. This is less likely to happen if you take it as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **If you took TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1 used for?

- the short-term relief of mild to moderate pain.

TEVA-LENOLTEC No. 1 should not be taken for pain for more than 5 days, unless directed by your healthcare professional.

How does TEVA-LENOLTEC No. 1 work?
TEVA-LENOLTEC No. 1 combines the effects of the pain reliever, codeine, which acts on the brain and spinal cord, with the pain reliever, acetaminophen. TEVA-LENOLTEC No. 1 also contains caffeine. Caffeine is a stimulant that increases activity in the brain and generally makes people feel more alert. It also affects the kidneys by causing an increased production of urine, and can increase your heart rate.

What are the ingredients in TEVA-LENOLTEC No. 1?
Medicinal ingredients: acetaminophen, caffeine and codeine phosphate.
Non-medicinal ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, silica colloidal anhydrous.

TEVA-LENOLTEC No. 1 comes in the following dosage forms:
Acetaminophen 300 mg, Caffeine 15 mg and Codeine Phosphate 8 mg, caplets or tablets.

Do not use TEVA-LENOLTEC No. 1 if:
- you are allergic to acetaminophen, caffeine, codeine or other opioids or any of the other ingredients in TEVA-LENOLTEC No. 1
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have asthma, trouble breathing, chronic lung disease or other chronic breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines or have been told that you are at risk for this
- you have severe pain in your abdomen
- you have a head injury
- you suffer from severe reduction in functions controlled by the brain such as breathing, heart rate and consciousness or you have increased pressure in your head or spinal cord
- you suffer from seizures
- you suffer from alcoholism or severe alcohol withdrawal
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- you are in labour
- you are breastfeeding

- you have serious liver or kidney 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 convert codeine into its active metabolite more rapidly and completely than other people (see ***Ultra-Rapid Metabolizers of Codeine***)
- you are less than 18 years old

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-LENOLTEC No. 1. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or consume 3 or more alcoholic beverages per day
- 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 thyroid, adrenal or prostate gland
- have difficulty urinating
- have, or had in the past hallucinations or other severe mental problems
- develop allergic reactions such as wheezing, rash or itching
- feel sedated or drowsy, are confused or have slow, shallow breathing
- have redness or swelling 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
- have pain that lasts more than 5 days or for fever more than 3 days
- have difficulty breathing, asthma or chronic lung disease
- are pregnant or are planning to get pregnant
- suffer from migraines
- are elderly or debilitated
- take tranquilizers, sedatives, sedating antihistamines or other depressants, salicylates, other pain and fever relief medications or nonsteroidal anti-inflammatory drugs (NSAIDs)
- take, or plan to take a serotonergic drug, or are not sure whether you are taking a serotonergic drug (e.g. anti-depressants, migraine medications)
- have recently had surgery under general anesthesia

Other Warnings you should know about:

Ultra-Rapid Metabolizers of Codeine:

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

Drug Abuse and Dependence and Tolerance
Like any opioid, if you use TEVA-LENOLTEC No. 1 for a long time, it may cause mental and physical dependence. Codeine also has the potential to cause addiction. There are important differences between physical dependence and addiction. If you use opioids for a long time, you may develop tolerance. This means that you may need higher doses of TEVA-LENOLTEC No. 1 to feel the same level of pain relief. It is important that you talk to your doctor if you have questions or concerns about addiction, physical dependence, or tolerance.

Your healthcare professional should give you TEVA-LENOLTEC No. 1 with the same level of caution as other oral opioid drugs. It is not recommended to use this drug for a long period of time.

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 TEVA-LENOLTEC No. 1 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.).

Pregnancy, nursing, labour and delivery: Do not use TEVA-LENOLTEC No. 1 while nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while it is still in the womb. TEVA-LENOLTEC No. 1 can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant, your doctor will determine if the benefits of using TEVA-LENOLTEC No. 1 outweigh the risks to your unborn baby. In addition, if you are pregnant and are taking this medication, it is important that you don't stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking TEVA-LENOLTEC No. 1. 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 TEVA-LENOLTEC No. 1.

TEVA-LENOLTEC No. 1 can cause:

- drowsiness
- dizziness or
- lightheadedness

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

Serotonin Syndrome: TEVA-LENOLTEC No. 1 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 TEVA-LENOLTEC No. 1 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.

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 you stop breathing from time to time while sleeping.

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. If you develop any of the above symptoms, seek medical help right away.

Worsened Pain: Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia), even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your doctor if you notice a change like this in your pain while you are taking TEVA-LENOLTEC No. 1.

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 medications may interact with TEVA-LENOLTEC No. 1:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking TEVA-LENOLTEC No. 1. 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 TEVA-LENOLTEC No. 1.
- 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 TEVA-LENOLTEC No. 1 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)
- drugs used to treat migraines (e.g., triptans)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin (such as COUMADIN®) and other anticoagulants (used for prevention or treatment of blood clots)
- anti-retroviral drugs (used to treat viral infections)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- some heart medication (such as beta blockers)
- St. John's Wort

How to take TEVA-LENOLTEC No. 1:
Use the smallest effective dose for the shortest period of time. Only take this medication when you need it, and never more often than every 4 to 6 hours.

Do not take with other drugs containing acetaminophen.

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

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

Usual dose (Adults ≥ 18 years of age):
TEVA-LENOLTEC No. 1 caplets or tablets:
Take 1 caplet/tablet every 4-6 hours as required, not to exceed 12 caplets/tablets in 24 hours. If pain does not respond to 1 caplet/tablet, take 2 caplets/tablets at next dose.

Overdose:

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

If you think you have taken too much TEVA-LENOLTEC No. 1, 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 TEVA-LENOLTEC No. 1?

These are not all of the possible side effects you may feel when taking TEVA-LENOLTEC No. 1. 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, or uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), or infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using TEVA-LENOLTEC No. 1.

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.			✓
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:

- TEVA-LENOLTEC No. 1 caplets and tablets: Protect from light. Store between 15°C – 30°C.
- Keep out of reach and sight of children.

If you want more information about TEVA-LENOLTEC No. 1:

- Talk to your healthcare professional
- Find the full Prescribing Information that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

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