PRESCRIBING INFORMATION

[N]TEVA-LENOLTEC No. 1

Acetaminophen, Caffeine and Codeine Phosphate Tablets

300 mg/ 15 mg / 8 mg

Tablets and Caplets

Opioid Analgesic -
Antipyretic

NOT A PRODUCT MONOGRAPH

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

www.tevacanada.com

Control: 222135

DATE OF REVISION:
June 5, 2019

PRESCRIBING INFORMATION

[N]TEVA-LENOLTEC No. 1

Acetaminophen, Caffeine and Codeine phosphate

Analgesic - Antipyretic

CLINICAL PHARMACOLOGY

TEVA-LENOLTEC products are analgesic, antipyretic agents.

ACTION

TEVA-LENOLTEC No.1, acetaminophen, caffeine and codeine phosphate tablets and caplets combine the analgesic effects of the centrally acting analgesic codeine, with a peripherally acting analgesic, 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.

Acetaminophen, codeine phosphate and caffeine are well absorbed orally.

Acetaminophen is distributed throughout most tissues of the body. **Acetaminophen** is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

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

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.

Pharmacokinetics

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

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 ($t_{1/2}$) 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. 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.

INDICATIONS AND CLINICAL USE

TEVA-LENOLTEC No.1

TEVA-LENOLTEC No.1 (acetaminophen, caffeine and codeine phosphate tablets and caplets) is indicated for the relief of mild to moderate pain associated with conditions such as headache, dental pain, myalgia, dysmenorrhea, pain following trauma, and pain following operative procedures.

TEVA-LENOLTEC No.1 (acetaminophen, caffeine and codeine phosphate tablets and caplets) may also be effective in relieving the pain associated with various forms of arthritis, but is not indicated as primary therapy for rheumatoid arthritis and similar inflammatory conditions.

Pediatrics (< 18 years of age)

Due to increased safety concerns with the use of codeine containing products in the pediatric population, TEVA-LENOLTEC No. 1 is not recommended for pediatric use. **(see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).**

CONTRAINDICATIONS

TEVA-LENOLTEC No.1 should not be administered to:

- Patients with severe liver or kidney impairment (see **WARNINGS AND PRECAUTIONS, Special Populations**, **Hepatic Insufficiency and Renal Insufficiency**)
- Patients with suspected surgical abdomen (e.g., acute appendicitis)
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type)
- Patients with acute asthma or other obstructive airway, or status asthmaticus
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, or cor pulmonale
- Patients with acute alcoholism, delirium tremens, or convulsive disorders
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, or head injury
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy)
- Women who are breastfeeding or during labour and delivery (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and Nursing Women**)
- Children less than 18 years old

TEVA-LENOLTEC No.1 (acetaminophen, caffeine and codeine phosphate tablets and caplets) should not be administered to patients who have previously exhibited hypersensitivity to caffeine, acetaminophen, codeine, or other opioids.

Codeine-containing products are contraindicated for postoperative pain management in children (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy.

WARNINGS AND PRECAUTIONS

General

TEVA-LENOLTEC No. 1 is contraindicated in patients with acute alcoholism since chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports usually involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose.

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.

Patients should be counselled to consult a physician before use if they are taking tranquilizers, sedatives, sedating antihistamines or other depressants, natural health products, prescription drugs, salicylates, any other pain and fever relief medication or nonsteroidal anti-inflammatory drugs (NSAIDS).

Keep out of the sight and reach of children.

Codeine is habit forming and potentially abusable. Consequently, the extended use of this product is not recommended.

TEVA-LENOLTEC No.1 tablets should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

Codeine products should be discontinued at the earliest sign of toxicity and medical help should be sought as soon as possible.

Head Injury and Increased Intracranial Pressure

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other opioids may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Opioids also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine should be used with caution in patients at risk for additive CNS effects (see **DRUG INTERACTIONS**). These products should not be used in patients with head injuries, convulsive disorders, or in conditions in which intracranial pressure is raised (see **CONTRAINDICATIONS**).

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**).

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). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine (see **Special Populations, Nursing Women**). Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see **CONTRAINDICATIONS**).

Respiratory

Codeine, including TEVA-LENOLTEC No.1, is not recommended for use in any patient in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, lung infections, multiple trauma or extensive surgical procedures.

Codeine produces dose-related respiratory depression. Caution should be exercised when acetaminophen with codeine is used postoperatively in patients with pulmonary disease or shortness of breath or whenever ventilatory function is depressed.

Patients should be counselled to consult a physician before use if they have difficulty breathing, have asthma or other chronic lung disease.

Gastrointestinal

Codeine or other opioids may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Codeine should not be used in patients with obstructive bowel disorders and in patients at risk of paralytic ileus (see **CONTRAINDICATIONS**).

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

Advise your patients to seek medical attention as soon as an acetaminophen overdose is suspected. Advise them not to wait for symptoms to appear (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

Hypersensitivity Reactions

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.

Occupational Hazards

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks. Patients using this drug should be cautioned about driving a car or operating potentially hazardous machinery if they become drowsy or show impaired mental or physical abilities while taking this medication.

The patient should understand the single-dose and 24-hour dose limits, and the time interval between doses. Like other narcotic-containing medications, these drugs are subject to the Controlled Drugs and Substances Act.

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.

Drug Abuse and Dependence

Codeine can produce drug dependence and has the potential for being abused. Tolerance, psychological and physical dependence may develop upon repeated administration of TEVA-LENOLTEC No.1 (acetaminophen, caffeine, and codeine phosphate tablets and caplets). These drugs should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid medications. The extended use of these products is not recommended.

Special Populations

Pregnant Women

There are no adequate and well-controlled studies of the combination of codeine and acetaminophen in pregnant women.

TEVA-Lenoltec No.1 (acetaminophen, caffeine and codeine phosphate tablets and caplets) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Codeine

Opioid analgesics cross the placental barrier. Neonates who have been exposed to codeine in utero can develop withdrawal syndrome (neonatal abstinence syndrome) after delivery. Cerebral infarction has been reported in this setting. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn.

Acetaminophen

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

Teratogenic Effects:

Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study, a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

Non-teratogenic Effects:

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

Nursing Women:
TEVA-LENOLTEC No.1 is contraindicated in women who are nursing (see **CONTRAINDICATIONS**).

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

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 potentially lead to serious adverse reactions, including death, in nursing infants** (see **WARNINGS AND PRECAUTIONS, Ultra-Rapid Metabolizers of Codeine**)**.**

Caffeine is distributed into the milk of nursing women.

Pediatrics:
TEVA-LENOLTEC No.1 contains codeine and should not be administered to children < 18 years of age (see **CONTRAINDICATIONS**).

Hepatic insufficiency:
Acetaminophen
TEVA-LENOLTEC No.1 is contraindicated in patients with severe liver failure. 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 liver disease, pain control may be compromised because codeine is not properly metabolized.

Renal Insufficiency:
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

The most frequently observed adverse effects include 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, 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.

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 (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

At higher doses, codeine has most of the disadvantages of morphine, including respiratory depression.

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.

DRUG INTERACTIONS

CNS depressants: Concomitant use with central nervous system depressants (e.g., barbiturates, chloral hydrate, benzodiazepines, phenothiazines, alcohol and centrally acting muscle relaxants) may cause additive CNS depression.

Opioid analgesics: Concurrent use with other opioid receptor agonists may cause additive CNS depression, respiratory depression and hypotensive effects.

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.

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.

Drug/Laboratory Test Interactions

Codeine may increase serum amylase levels.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In Case of Overdose: Call a Poison Control Centre or doctor immediately, even if you do not notice any signs or symptoms such as increased sweating, nausea, vomiting, stomach pain or loss of appetite.

Acetaminophen:

In adults and adolescents (≥ 12 years of age), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 grams 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 grams. 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.

The following are 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:
Anorexia
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 phosphate increased, Blood lactate increased

The following clinical events 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 renal failure
General Disorders and Administration Site Conditions:
Multi-organ failure

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.

General Management: 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:

Risks of codeine overdose include asthenia, cardiorespiratory arrest, cerebral edema, coma, confusional state, convulsion, 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.

General Management: 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

General Management: 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TEVA-LENOLTEC No.1 should not be used in children less than 18 years old (see **CONTRAINDICATIONS**).

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, Hepatic).**

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 (acetaminophen, caffeine and codeine phosphate) 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.

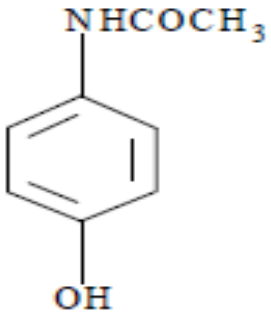
Based on the dosage guidance, the number of tablets per dose, and the maximum number of tablets per 24 hours, should be conveyed in the prescription.

PHARMACEUTICAL INFORMATION

Drug Substance: **Acetaminophen**

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

Structural formula:



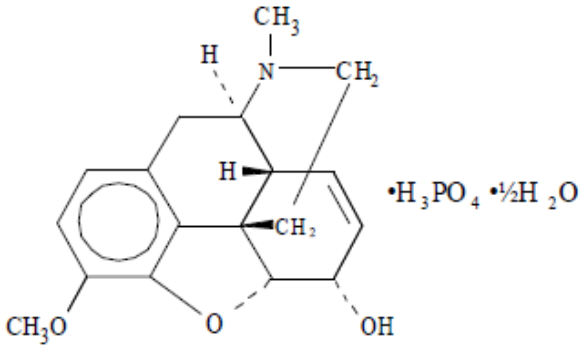
Molecular Formula: $C_8H_9NO_2$

Molecular Weight: 151.2 g/mol

Drug Substance: **Codeine Phosphate**

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

Structural formula:



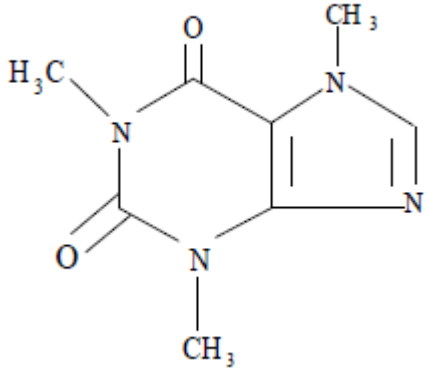
Molecular Formula: $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$

Molecular Weight: 406.4 g/mol

Drug Substance: **Caffeine**

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

Structural formula:



Molecular Formula: $C_8H_{10}N_4O_2$

Molecular Weight: 194.19 g/mol

STORAGE AND STABILITY

TEVA-LENOLTEC No. 1 caplets and tablets: Store between 15^0C – 30^0C.

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.

REFERENCES

Prescribing Information for TYLENOL with Codeine No. 2, TYLENOL with Codeine No. 3 and TYLENOL with Codeine No. 4, Control No. 182927, 182928, Date of revision February 15, 2016.

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

[N]TEVA-LENOLTEC No. 1

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.

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:

TEVA-LENOLTEC No. 1 tablets contain acetaminophen, caffeine and codeine phosphate.

Non-medicinal ingredients:

TEVA-LENOLTEC No. 1 tablets also contain 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:

- have serious liver or kidney problems;
- have severe abdominal pain;
- have bowel blockage or narrowing of the stomach or intestines or have been told that you are at risk for this;
- suffer from severe asthma or breathing problems;
- 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;

- suffer from alcoholism, severe alcohol withdrawal or have a seizure disorder;
- suffer from severe reduction in functions controlled by the brain such as breathing, heart rate and consciousness, or if you have a head injury or increased pressure in your head or spinal cord;
- are taking monoamine oxidase (MAO) inhibitors or have taken an MAO inhibitor in the last 14 days;
- are about to go into labour or are breastfeeding;
- are less than 18 years old;
- are less than 18 years old and are having (or have recently had) your tonsils or adenoids removed;
- are allergic to acetaminophen, codeine or other opioids or if you are allergic to caffeine.

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:

- 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 liver or kidney problems;
- have difficulty breathing, asthma or chronic lung disease;
- are pregnant or are planning to get pregnant;
- consume 3 or more alcoholic beverages per day;
- are elderly or debilitated;
- have an underactive thyroid, difficulty urinating, adrenal gland problems such as Addison's disease, or an enlarged prostate;
- take tranquilizers, sedatives, sedating antihistamines or other depressants, salicylates, other pain and fever relief medications or nonsteroidal anti-inflammatory drugs (NSAIDs);
- have recently had surgery under general anaesthesia.

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:
Codeine can produce drug dependence and has the potential for being abused. Tolerance, psychological and physical dependence may develop over time with repeated use of TEVA-LENOLTEC No. 1. Your healthcare professional should prescribe and administer TEVA-LENOLTEC No. 1 with the same degree of caution appropriate to the use of other oral opioid medications. Using these products for a prolonged period of time is not recommended.

Serious skin reactions (Stevens - Johnson Syndrome, Toxic Epidermal Necrolysis, Hypersensitivity Syndrome):
Acetaminophen can cause serious skin reactions that can spread to your mouth, lips, face, hands, trunk, arms and legs. This condition is life-threatening. Stop taking 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.).

Driving or operating machinery:
Do not drive a car or operate other potentially hazardous machinery until you are sure that taking TEVA-LENOLTEC No. 1 does not make you drowsy.

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:

- barbiturates, chloral hydrate, benzodiazepines, phenothiazines, alcohol and centrally acting muscle relaxants;
- other products containing acetaminophen;
- other opioid analgesics;
- blood-thinners (warfarin-type anticoagulants);
- quinidine, methadone and paroxetine.

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.**

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.**

Overdose symptoms include extreme sleepiness, confusion, or shallow breathing.

In Case of Overdose: 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 you do not notice any signs or symptoms such as increased sweating, nausea, vomiting, stomach pain or loss of appetite.

What are possible side effects from using TEVA-LENOLTEC No. 1?
These are not all 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. Please also see section **To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-LENOLTEC No. 1.**

The most frequent side effects include drowsiness, light-headedness, dizziness, shortness of breath, nausea and vomiting.

Other side effects include feelings of extreme happiness or unhappiness, constipation, abdominal pain, itching and rash.

Side effects related to the caffeine in TEVA-LENOLTEC No. 1 include insomnia, restlessness, nervousness and mild delirium, nausea, vomiting and stomach irritation.

TEVA-LENOLTEC No. 1 can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

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			
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			
Respiratory Depression: slow, shallow or weak breathing.			✓
Severe Allergic Reactions: swelling of face, eyes, lips, or tongue, trouble swallowing or breathing, skin rash.			✓
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: Store between 15^0C – 30^0C.

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://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9.

Last revised: June 5, 2019