PRESCRIBING INFORMATION

[N]TEVA-CODEINE
Codeine phosphate tablets USP

15 mg and 30 mg Tablets

Opioid analgesic/Antitussive

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

www.tevacanada.com

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablets	microcrystalline cellulose, lactose, stearic acid, magnesium stearate, silicon dioxide. Sulfite-sodium-Parabens-Gluten-Free.

INDICATIONS AND CLINICAL USE

Adults
TEVA-CODEINE is indicated for the symptomatic treatment of mild to moderate pain of various causes and the control of exhausting, nonproductive cough which does not respond to non-opioid antitussives. **TEVA-CODEINE** is not indicated as an as-needed (prn) analgesic.

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

Pediatrics (< 12 years of age)
Regardless of clinical setting, the use of codeine is contraindicated in patients below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics; and DOSAGE AND ADMINISTRATION**).

Pediatrics (12 - 18 years of age)
The safety and efficacy of TEVA-CODEINE has not been studied in the pediatric population. Therefore, the use of TEVA-CODEINE is not recommended in patients over 12 and under 18 years of age

CONTRAINDICATIONS
Patients who are hypersensitive to the active substance codeine phosphate or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE**

FORMS, COMPOSITION AND PACKAGING section of the Prescribing Information.

- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- CYP2D6 ultra-rapid metabolizers who convert codeine into its active metabolite more rapidly and completely than other people (see **WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-Rapid Metabolizers of Codeine**; and **OVERDOSAGE, Symptoms** and **Treatments**)
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant or during labour and delivery. (see **SERIOUS WARNINGS AND PRECAUTIONS, and WARNINGS AND PRECAUTIONS**)
- Pediatric patients <12 years of age
- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

<u>Limitations of Use</u>
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-CODEINE (codeine phosphate) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

<u>Addiction, Abuse, and Misuse</u>
TEVA-CODEINE poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing TEVA-CODEINE, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). TEVA-CODEINE should be stored securely to avoid theft or misuse.

SERIOUS WARNINGS AND PRECAUTIONS

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of TEVA-CODEINE. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of TEVA-CODEINE or following a dose increase.

Tablets: **TEVA-CODEINE must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving TEVA-CODEINE 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-CODEINE, especially by children, can result in a fatal overdose of codeine phosphate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of TEVA-CODEINE 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-CODEINE should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of TEVA-CODEINE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

General

Patients should be instructed not to give TEVA-CODEINE (codeine phosphate) tablets to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. TEVA-CODEINE should be stored securely to avoid theft or misuse.

TEVA-CODEINE should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking **TEVA-CODEINE** as it may increase the chance of experiencing serious adverse events, including death.

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

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

Abuse and Misuse

Like all opioids, **TEVA-CODEINE** is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, **TEVA-CODEINE** should be prescribed and handled with caution.

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

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

Cardiovascular

Codeine phosphate administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of TEVA-CODEINE.

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

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of TEVA-CODEINE and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).**

Use in Drug and Alcohol Addiction

TEVA-CODEINE 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-CODEINE; extreme caution and awareness is warranted to mitigate the risk .

Gastrointestinal Effects

Codeine phosphate and other morphine-like opioids have been shown to decrease bowel motility. Codeine phosphate may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of **TEVA-CODEINE** is contraindicated in pregnant women (see C**ONTRAINDICATIONS**).

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): TEVA-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-CODEINE** 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-CODEINE 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.

Serotonin Syndrome: TEVA-CODEINE could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotoninergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. TEVA-CODEINE should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John’s Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Head Injury: The respiratory depressant effects of codeine phosphate, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, codeine phosphate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, codeine phosphate must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS).**

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

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-CODEINE 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-CODEINE for at least 24 hours before the operation and TEVA-CODEINE 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-CODEINE** is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Codeine phosphate and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

TEVA-CODEINE 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-CODEINE may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of codeine phosphate with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Codeine phosphate should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS)**.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of TEVA-CODEINE, 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-CODEINE 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-CODEINE are essential. Overestimating the TEVA-CODEINE dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**).

Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome (see **CONTRAINDICATIONS**).

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory

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

Sensitivity/Resistance

Pruritus, urticaria, other skin rashes, edema, diaphoresis, wheal and flare over the vein with i.v. injection. Because of close structural similarities, patients exhibiting systemic allergy to morphine (e.g., generalized rash, shortness of breath) should not receive codeine, diamorphine, hydromorphone, oxycodone or oxymorphone.

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.

Special Populations

Special Risk Groups: Codeine phosphate should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women:

Studies in humans have not been conducted. TEVA-CODEINE crosses the placental barrier and is contraindicated in pregnant women.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-marketing Experience**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women:

Since opioids can cross the placental barrier and are excreted in breast milk, TEVA-CODEINE is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opiods, should be readily available if TEVA-CODEINE is used in this population.

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

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

Pediatrics (< 12 years of age): Regardless of clinical setting, the use of codeine is contraindicated in patients below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see **CONTRAINDICATIONS**).

Pediatrics (12-18 years of age): The safety and efficacy of codeine has not been studied in the pediatric population. Therefore, use of codeine is not recommended in patients over 12 and under 18 years of age.

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

Patients with Hepatic and/or Renal Impairment:
Codeine should be given with caution and the initial dose should be reduced in certain patients such as the debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture (see **DOSAGE AND ADMINISTRATION**.

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**)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of TEVA-CODEINE (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 TEVA-CODEINE are:
Sedation, nausea and vomiting, constipation and sweating. These effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated if the patient lies down.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with opioid analgesics and include those reported in TEVA-CODEINE clinical trials, whether related or not to codeine phosphate.

Cardiovascular: Supraventricular tachycardia, bradycardia, palpitations, faintness, syncope, postural hypotension and hypertension, and phlebitis following i.v. injection.

Gastrointestinal: Dry mouth, nausea, vomiting, constipation, biliary tract spasm, laryngospasme, anorexia, diarrhea, cramps, dyspepsia, taste alterations.

General and CNS: Drowsiness, sedation, euphoria, dysphoria, weakness, headache, agitation, seizures, uncoordinated muscle movements, alterations of mood, dreams, hallucinations and disorientation, visual disturbances, insomnia, miosis, toxic psychoses.

Genitourinary: Urinary retention or hesitance, antidiuretic effect, reduced libido and/or potency.

Respiratory:
Codeine, including TEVA-CODEINE 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.

Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of the cough is identified, that modification of the cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

Use with extreme caution in patients having an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve and patients with preexisting respiratory depression, hypoxia or hypercapnia. Usual therapeutic doses may decrease respiratory drive while simultaneously, increasing airway resistance to the point of apnea. In patients with asthma or pulmonary emphysema, codeine may, due to its drying action on the respiratory mucosa, increase viscosity of bronchial secretions and suppress the cough reflex.

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

The respiratory depressant effects of codeine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury or intracranial lesions or pre-existing increase in intracranial pressure. Opioids produce adverse reactions which may obscure the clinical course of a patient with head injuries. In such patients, codeine must be used with extreme caution and only if its use is deemed essential.

Use with caution in patients with seizures as they may be exacerbated or induced by opioids.
Use with caution in patients with cardiac arrhythmias due to the cholinergic effects of the

drug. Codeine should be given with caution and the initial dose should be reduced in certain patients such as the debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Hypersensitivity:
Pruritus, urticaria, other skin rashes, edema, diaphoresis, wheal and flare over the vein with i.v. injection. Because of close structural similarities, patients exhibiting systemic allergy to morphine (e.g., generalized rash, shortness of breath) should not receive codeine, diamorphine, hydromorphone, oxycodone or oxymorphone.

Nausea and Vomiting:
Occur frequently after single doses of narcotics or as an early unwanted effect of regular opioid analgesic therapy.

Withdrawal Syndrome:
Physical dependence with or without psychological dependence tends to occur with chronic administration. An abstinence syndrome may be precipitated when an opioid analgesic is abruptly discontinued or opioid antagonists are administered. The following withdrawal symptoms may be observed after abrupt discontinuation of an opioid analgesic: body aches, diarrhea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, sleep disturbances, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use and gradual withdrawal from opioid analgesics, these symptoms are usually mild.

Other:
Abnormal liver function test results (propoxyphene flushing/warmth).

Post-Marketing Experience:
Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Serious Drug Interactions

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

Overview
Interaction with Central Nervous System (CNS) Depressants:

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

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

Drug-Drug Interactions

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

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

CNS Agents:
Concomitant administration of other CNS drugs such as sedatives, hypnotics, phenothiazines, anesthetics and alcohol may increase the sedative and depressant effects of opioid analgesics. If the concomitant use of these drugs is considered necessary, their doses should be reduced accordingly.

MAO Inhibitors:
Serious adverse reactions have been reported in patients who receive MAO inhibitors with pethidine. Other opioid analgesics should be used with extreme caution, if at all, in patients taking MAO inhibitors (including selegiline) or within 14 days of such therapy.

Opioid Antagonists:
Naltrexone and agonist-antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol) should not be administered to a patient who has received or is receiving a course of therapy with

a pure opioid agonist analgesic. In these patients, mixed agonist-antagonists may reduce the analgesic effect or may precipitate withdrawal symptoms.

Other Opioids:
The use of more than one opioid agonist at a time is usually inappropriate; additive CNS depressant, respiratory depressant and hypotensive effects may occur if 2 or more agonists are used concurrently. Potentiation of effects may occur with a previously administered long-acting opioid analgesic.

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

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

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

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

DOSAGE AND ADMINISTRATION

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

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

Children under 12: Codeine is contraindicated in children less than 12 years old because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see **INDICATIONS**).

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

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For pain management, the maximum recommended daily dose of TEVA-CODEINE is 360 mg (54 morphine milligram equivalent). For cough management, the maximum recommended daily dose of TEVA-CODEINE is 120 mg (18 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing TEVA-CODEINE as the likelihood of experiencing serious adverse events can

depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of TEVA-CODEINE (see DOSAGE AND ADMINISTRATION - Adjustment or reduction of Dosage).

Dosing Considerations

TEVA-CODEINE (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-CODEINE is not indicated for rectal administration.

TEVA-CODEINE may be taken with or without food with a glass of water.

The dose initiation should follow a conservative approach in certain patients such as the debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

The recommended adult starting dose in these patients should be at 1/3 to 1/2 the usual starting dose followed by careful dose titration to adequate pain control according to their clinical situation.

Recommended Dose and Dosage Adjustment

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

15 and 30 mg tablets:

Adults:

Analgesia: 15 to 60 mg every 4 to 6 hours as necessary.

Antitussive:

15 to 30 mg every 6 to 8 hours as necessary to a maximum of 120 mg daily.

Doses should be adjusted in renal failure: For creatinine clearance of 10 to 50 mL/min, decrease the dose by 25% and titrate. If creatinine clearance is less than 10 mL/min, decrease the dose by 50% and titrate.

Patients not Receiving Opioids at the Time of Initiation of Codeine Treatment: The usual initial adult dose of **TEVA-CODEINE** for patients who have not previously received opioid analgesics is 15 to 30 mg, orally, every 4 to 6 hours as necessary.

Patients Currently Receiving Opioids

For patients who are currently receiving other opioids, please refer to the following table to determine the approximate analgesic equivalences of various opioid analgesics.

Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50% to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 1: Opioid Conversion Table

Opioids	To convert to oral morphine equivalent	To convert from oral morphine multiply by	90 MED equivalent dose
Morphine	1	1	90 mg/d
Codeine	0.15	6.67	600 mg/d
Hydromorphone	5	0.2	18 mg/d
Oxycodone	1.5	0.667	60 mg/d
Tapentadol	0.3 – 0.4	2.5 – 3.33	300 mg/d
Tramadol	0.1 – 0.2	6	*
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.**
Busse J. The 2017 Canadian guideline for opioids for chronic non-cancer pain. Hamilton (ON): McMaster University; 2017

Geriatrics:
Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. TEVA-CODEINE should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Use with Non-Opioid Medications:
If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. **TEVA-CODEINE** can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration:
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including **TEVA-CODEINE**. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

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

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

Symptoms:
euphoria, dysphoria visual disturbances, hypotension and coma or death from respiratory depression.

Treatment:

Symptomatic and supportive therapy. Maintain ventilation and administer oxygen as needed. The opioid antagonist naloxone should be administered. If the patient is conscious and has not lost the gag reflex, empty the stomach by inducing emesis with ipecac syrup. If the patient is extremely drowsy, unconscious, convulsing or has no gag reflex, perform gastric lavage. Follow with activate charcoal (50 to 100 g in adults) and a cathartic.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Codeine exerts its effect on opiate receptors, primarily in the CNS and smooth muscle. Its effects include: analgesia, respiratory depression, suppression of the cough reflex, decreased gastrointestinal motility. CNS changes and stimulation of the chemoreceptor trigger zone which causes nausea and vomiting.

Pharmacokinetics:

Codeine is well absorbed orally and from parenteral sites. Onset of analgesic action occurs in 10 to 30 minutes after parenteral administration or in up to 45 minutes following an oral dose. Peak effect is reached in 30 to 60 minutes after an i.m. or s.c. dose or 1 to 2 hours after oral dosing. Analgesia lasts 4 to 6 hours. Codeine's antitussive effect peaks within 1 to 2 hours and lasts up to 4 hours. Its plasma half-life is approximately 3 to 4 hours but may be as long as 19 hours in anephric patients. Codeine is approximately 7% bound to plasma protein; its volume of distribution is 2.5 to 3.5 L/kg. It is primarily metabolized by the liver, and its metabolites, some active, are eliminated in the urine. Only a small fraction (0.01) is excreted unchanged.

See Annex 1 (opioid analgesics: approximate analgesic equivalence) for the opioid analgesic response equivalent to that from 10 mg of morphine.

Central Nervous System:

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

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

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

Gastrointestinal Tract and Other Smooth Muscle: Codeine phosphate causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased

to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

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

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

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

Special Populations and Conditions
Pediatrics: The use of codeine is contraindicated in patients below the age of 12 years due to increased safety concerns (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

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

STORAGE AND STABILITY

Store between 15-30 C·

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-CODEINE 15 mg: each white tablet contains 15 mg of codeine phosphate. Also contains as non-medicinal ingredients: microcrystalline cellulose, lactose, stearic acid, magnesium stearate, dioxide silicon. Sulfite-Sodium-Parabens-Gluten-Free. Bottles of 100 tablets.

TEVA-CODEINE 30 mg: each white tablet contains 30 mg of codeine phosphate. Also contains as non-medicinal ingredients: microcrystalline cellulose, lactose, stearic acid, magnesium stearate, silicon dioxide. Sulfite-sodium-Parabens-Gluten-Free. Bottles of 100 and 500 tablets.

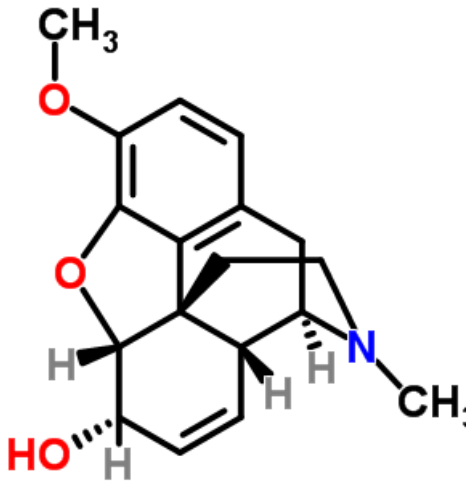
Store between 15-30°C.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name:	**Codeine phosphate**
Chemical name:	Morphinan-6-ol,7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5α, 6α)-, phosphate (1:1) (salt).
Molecular formula:	$C_{18}H_{24}NO_7P$
	C54.41%, H6.09%, N3.53%, O28.18%, P7.79%

Structural formula**: {CNSD: Please include a proper structural formula**



Molecular weight:	397.37
Physical state:	Hemihydrate, fine, white, needle-shaped crystals; a crystalline powder; odourless, affected by light.
Solubility:	Freely soluble in water, very soluble in hot water, slightly soluble in alcohol, more soluble in boiling alcohol.

ANNEX 1
OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES[1]

Drug	Equivalent dose (mg) [2] Compared to morphine 10 mg IM)		Duration of Action (Hours)
Strong Opioid Agonists			
Morphine (single dose)	10	60	3-4
(chronic dose)	10	20-30[3]	3-4
Hydromorphine	1.5-1	6-7.5	2-4
Anileridine	25	75	2-3
Levophanol	2	4	4-8
Meperidine[1]	75	300	1-3
Oxymorphone	1.5	5(rectal)	3-4
Methadone[2]			
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Oxycodone	5-10	10-15	2-4
Propoxyphene	50	100	2-4
Mixed Agonist Antagonists[3]			
Pentazocine[1]	60	180	3-4
Nalbuphine	10		3-6
Butorphanol	2		3-4

[1] Most of these data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.

[2] For acute pain, the oral dose of morphine is six times the injectable dose. However, for chronic dosing, this ration becomes 2 or 3: 1, possibly due to the accumulation of active metabolites.

[3] These drugs are not recommended for the management of chronic pain.

REFERENCES

1. Cancer Pain: A monograph on the Management of Cancer Pain, Health and WelfareCanada 1984.

2. Foley, K.M. New Engl. J. Med. 313: 84-95, 1985. Aronoff, G.M. and Evans, W.O., In: Evaluation and Treatment of chronic Pain 2nd Ed., G.M. Aronoff (Ed.), Williams and Wilkins, Baltimore, pp. 359-368 1992.

3. Cheerny, N.I. and Portenoy, R.K., In:Textbook of Pain, 3rd Ed., P.D. Wall and R. Melzack (Eds.), Churchill Livingstone, London, pp. 1437-1467, 1994.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION
^{N}TEVA-CODEINE
Codeine phosphate Tablets

Read this carefully before you start taking **TEVA-CODEINE** 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-CODEINE**.

Serious Warnings and Precautions

- **Even if you take TEVA-CODEINE as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**

- **When you take TEVA-CODEINE it must be swallowed whole. Do not cut, break, crush, chew, dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**

- **You may get life-threatening breathing problems while taking TEVA-CODEINE. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**

- **You should never give anyone your TEVA-CODEINE. They could die from taking it. If a person has not been prescribed TEVA-CODEINE, taking even one dose can cause a fatal overdose. This is especially true for children.**

- **If you took TEVA-CODEINE 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-CODEINE 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-CODEINE used for?
TEVA-CODEINE is used for adults to relieve:
- mild to moderate pain of various causes
- non-productive cough that does not respond to other cough medicines

Your pain may increase or decrease from time to time and your doctor may need to change the amount of codeine you take daily (daily dosage).

How does TEVA-CODEINE work?
Codeine belongs to a class of drugs which is commonly referred to as opiates, opioids or narcotics, and also includes fentanyl, hydromorphone, morphine and oxycodone.

TEVA-CODEINE is a painkiller belonging to the class of drugs known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in TEVA-CODEINE?
Medicinal ingredients: Codeine phosphate

Non-medicinal ingredients:
Tablets - microcrystalline cellulose, lactose, stearic acid, magnesium stearate, dioxide silicon. Sulfite- Sodium-Parabens-Gluten-Free.

TEVA-CODEINE comes in the following dosage forms:
Tablet: 15mg and 30 mg

Do not use TEVA-CODEINE if:
- your doctor did not prescribe it for you;
- your pain is mild;
- you are allergic to codeine phosphate or any of the other ingredients in TEVA-CODEINE
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen, or are at risk of blocked intestines;
- you had surgery less than 24 hours ago;

- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- have been told by your doctor that you break down codeine rapidly. This can lead to codeine overdose even at the usual adult dose
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding. The use of codeine-containing products while breast-feeding may harm your baby. If you breastfeed and take TEVA-CODEINE, seek immediate medical care for your baby if they are overly drowsy, sedated, have difficulty breast-feeding, have breathing difficulties, and are floppy (have decreased muscle tone). This is very serious for the baby and can lead to death. Tell the baby's doctor that you are breastfeeding and took TEVA-CODEINE.
- you are less than 12 years old
- you are less than 18 years old and are having (or have recently had) your tonsils or adenoids removed because of frequent interruption of breathing during sleep

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-CODEINE. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- are pregnant or planning to become pregnant
- are suffer from migraines
- are planning to become pregnant

Other warnings you should know about:
Some people metabolize codeine at a much faster rate than the general population, which may lead to accidental overdose, if this should happen to you, seek help immediately (see Overdose, for symptoms of overdose and what to do if it happens). If you know that you metabolize codeine rapidly, tell your doctor BEFORE starting this medication.

TEVA-CODEINE is not recommended for anyone who has or is at risk for breathing problems such as:

- lung infections, or respiratory conditions
- neuromuscular disorders
- severe heart problems
- recent multiple traumas or extensive surgical procedures

Opioid dependence and addiction:
There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

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

If you are pregnant and are taking TEVA-CODEINE, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking TEVA-CODEINE. 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-CODEINE. TEVA-CODEINE can cause:

- drowsiness
- dizziness or
- lightheadedness

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

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off TEVA-CODEINE.

Serotonin Syndrome: TEVA-CODEINE 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-CODEINE with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TEVA-CODEINE:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking TEVA-CODEINE. 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-CODEINE
- 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-CODEINE with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- drugs used to treat migraines (e.g. triptans)
- warfarin (such as coumadin) and other anticoagulants (used for prevention or treatment of blood clots)
- 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)
- grapefruit juice
- St. John's Wort

How to take TEVA-CODEINE:

TEVA-CODEINE tablets must be swallowed whole and should not be chewed, dissolved or crushed, since this can cause the release of too much codeine that can seriously harm you. The 30 mg strength has a score line to facilitate halving, if directed by your doctor. The half tablets should also be swallowed intact.

You should not consume alcohol while taking TEVA-CODEINE, as it may increase the chance of experiencing dangerous side effects.

Keep TEVA-CODEINE out of sight and reach of children. You should not give TEVA-CODEINE to anyone as inappropriate use may have severe medical consequences, including death.

Usual Adult Starting Dose:
Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take TEVA-CODEINE for up to 7 days. If you need to take TEVA-CODEINE for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

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

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

TEVA-CODEINE is not recommended for rectal administration.

Usual dose (Adults):
Pain:
Tablets: 15 to 60 mg every 4 to 6 hours if necessary.

Cough:
Tablets: 15 to 30 mg every 6 to 8 hours if necessary to a maximum of 120 mg daily.

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

Stopping your Medication

If you have been taking TEVA-CODEINE for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking TEVA-CODEINE. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing

- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking TEVA-CODEINE.

Refilling your Prescription for TEVA-CODEINE:
A new written prescription is required from your doctor each time you need more TEVA-CODEINE. Therefore, it is important that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much TEVA-CODEINE, 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-CODEINE?
These are not all the possible side effects you may feel when taking TEVA-CODEINE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Drowsiness

- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using TEVA-CODEINE.

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		√	

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	
Heartbeat: heart palpitations.			
Low Blood Pressure: dizziness, fainting, light-headedness.	√		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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:

- Store at room temperature 15 – 30°C. Keep in a dry place.
- **Keep unused or expired TEVA-CODEINE in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep TEVA-CODEINE under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes TEVA-CODEINE, get emergency help right away.**

Disposal:

TEVA-CODEINE should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about TEVA-CODEINE:

- Talk to your healthcare professional

- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); 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

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