PRESCRIBING INFORMATION

[N]TEVA-COTRIDIN

Triprolidine hydrochloride 2 mg / 5 mL –
Pseudoephedrine hydrochloride 30 mg / 5 mL – Codeine phosphate 10 mg / 5 mL

[N]TEVA-COTRIDIN EXPECTORANT

Triprolidine hydrochloride 2 mg / 5 mL – Pseudoephedrine hydrochloride
30 mg / 5 mL – Guaifenesin 100 mg / 5 mL – Codeine phosphate 10 mg / 5 mL

Antihistamine – Antitussive Decongestant

Syrups

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	2 mg triprolidine hydrochloride, 30 mg pseudoephedrine hydrochloride, 10 mg codeine phosphate, in 5 mL of syrup	Amaranth, artificial flavourings, glycerin, methylparaben, propylparaben, purified water, sorbitol solution and sucrose.
Oral	2 mg triprolidine hydrochloride, 30 mg pseudoephedrine hydrochloride, 100 mg guaifenesin, 10 mg codeine phosphate, in 5 mL of syrup	Artificial flavourings, citric acid, FD&C yellow #6, maltitol solution, menthol, methylparaben, polyethylene glycol, propylene glycol, propylparaben, purified water, sodium citrate and sodium cyclamate.

INDICATIONS AND CLINICAL USE

Adults
TEVA-COTRIDIN (triprolidine hydrochloride / pseudoephedrine hydrochloride / codeine phosphate) and TEVA-COTRIDIN EXPECTORANT (triprolidine hydrochloride / pseudoephedrine hydrochloride / guaifenesin / codeine phosphate) are indicated for the temporary relief of coughs associated with allergy or the common cold.

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

Pediatrics (< 18 years of age)
Regardless of the clinical setting, codeine, including TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT, must not be used in patients below the age of 18 years due to increased safety concerns (see **WARNINGS AND PRECAUTIONS; Special Populations; Pediatrics (< 18 years of age)).**

CONTRAINDICATIONS

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups are contraindicated in:

- Patients under the age of 18 years (see **WARNINGS AND PRECAUTIONS; Special Populations; Pediatrics (< 18 years of age)**).
- Women who are breastfeeding, pregnant, or during labour and delivery (see **SERIOUS WARNINGS AND PRECAUTIONS**, and **WARNINGS AND PRECAUTIONS**).
- Patients who are known to be CYP2D6 extensive or ultra-rapid metabolizers for whom there is an increased risk of developing symptoms of opioid toxicity, even at commonly prescribed doses (see **WARNINGS AND PRECAUTIONS, Ultra-Rapid Metabolizers of Codeine**). General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression which may be life-threatening and very rarely fatal.
- Patients who are hypersensitive to the active substances: codeine phosphate or other opioid analgesics; triprolidine hydrochloride or other antihistamines of similar chemical structure; sympathomimetic amines including pseudoephedrine hydrochloride; guaifenesin; or to any ingredient in the formulation. Both TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT contain methylparaben and propylparaben. It is contraindicated in patients with hypersensitivity to parabens. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy). The concomitant use of pseudoephedrine and this type of product may cause a rise in blood pressure. In addition, the concomitant use of a codeine-containing product and monoamine oxidase inhibitors can occasionally result in symptoms such as hyperpyrexia, arrhythmia, myoclonus or coma.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with chronic or persistent cough, such as what occurs with asthma, smoking or emphysema, or where cough is accompanied by excessive secretions (e.g. bronchiectasis).
- Patients receiving any other sympathomimetics, such as decongestants, appetite suppressants, and amphetamine-like psychostimulants.

- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with hypertension or coronary artery disease.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe hepatic impairment, as it may precipitate hepatic encephalopathy.
- Patients with moderate to severe renal impairment (glomerular filtration rate less than 60 mL/min).
- Patients with pheochromocytoma.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- 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 ulcerative colitis, since in common with other opioid analgesics, codeine may precipitate toxic dilatation or spasm of the colon.
- Codeine in common with other centrally acting antitussive agents should not be given to patients in, or at risk of developing respiratory failure.

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-COTRIDIN (triprolidine hydrochloride / pseudoephedrine hydrochloride / codeine phosphate) or TEVA-COTRIDIN EXPECTORANT (triprolidine hydrochloride / pseudoephedrine hydrochloride / guaifenesin / codeine phosphate) Syrups should only be used in patients for whom alternative non-opioid treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate cough management (see DOSAGE AND ADMINISTRATION).

<u>Addiction, Abuse, and Misuse</u>
TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups 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-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS, Abuse and Misuse). TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups should be stored securely to avoid theft or misuse.

<u>Life-threatening Respiratory Depression: OVERDOSE</u>
Serious, life-threatening, or fatal respiratory depression may occur with use of TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups. 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-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups or following a dose increase. Further, instruct patients of the hazards related to taking opioids, including fatal overdose.

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). Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.

- **Reserve concomitant prescribing of TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups 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
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 physiological complications, and that appropriate therapy for the primary disease is provided.

Accidental ingestion, especially by children can result in a fatal overdose of codeine (see DOSAGE AND ADMINISTRATION, disposal, for instructions on proper disposal).

Patients should be advised to seek medical advice if symptoms persist for more than 3 days.

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

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT should not be used in patients with a history of arrhythmia, epilepsy, increased intraocular pressure (narrow angle glaucoma), prostatic hypertrophy, bladder neck obstruction, diabetes mellitus, cardiovascular disease and hyperthyroidism, unless its benefits outweigh its risks in these patients.

TEVA-COTRIDIN Syrup contains 2.5 g of sucrose per 5 mL. TEVA-COTRIDIN should be used with considerable caution in patients with diabetes mellitus.

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT should be prescribed with caution for certain special at risk patients such as the elderly and debilitated, for those with gallbladder disease or gallstones, history of bronchial asthma, or urethral stricture.

Patients' self-medication should be assessed. TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT should not be used by patients intolerant to sympathomimetics used for the relief of nasal or sinus congestion. Such drugs include ephedrine, epinephrine, phenylpropanolamine and

phenylephrine. Symptoms of intolerance include drowsiness, dizziness, weakness, difficulty in breathing, tenseness, muscle tremors or palpitations.

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT should be used with caution in patients taking the following medications: metoclopramide, domperidone, and central nervous system depressants, including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazine (see **DRUG INTERACTIONS**).

Abuse and Misuse

Like all opioids, TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT are potential drugs of abuse and misuse, which can lead to overdose and death. Therefore, TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should be prescribed and handled with caution.

Use in Drug and Alcohol Addiction

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT are opioids with no approved use in the management of pain. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of cough requiring opioids. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT; extreme caution and awareness is warranted to mitigate the risk.

Carcinogenesis and Mutagenesis

See **TOXICOLOGY** section.

Cardiovascular

Codeine administration may result in hypotension and dizziness. TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT should be used with caution in patients taking beta-blockers or other anti-hypertensives.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT and there is a potential for development of psychological dependence. Patients should take the drug only for as long, in the amounts, and as frequently as prescribed.

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.

Endocrine

Adrenal Insufficiency

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

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

Gastrointestinal Effects
TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT should not be used in patients with obstructive bowel disorder or acute abdominal conditions (i.e. acute appendicitis or pancreatitis), stenosing peptic ulcer or pyloroduodenal obstruction, unless its benefits outweigh its risks in these patients.

Patients with a history of cholecystectomy should consult a doctor before using combination products of Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Codeine phosphate and Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Guaifenesin-Codeine phosphate as they may cause acute pancreatitis in some patients.

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

There have been reports of ischemic colitis with pseudoephedrine. TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should be discontinued immediately and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischemic colitis develop.

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

Immune
Large doses of codeine may cause the release of significant quantities of histamine, which may be associated with hypotension, cutaneous vasodilation, urticaria and, more rarely, bronchoconstriction.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Use of TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT are contraindicated in pregnant women (see **CONTRAINDICATIONS**).

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.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Concomitant use of opioids, including TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT, with benzodiazepines, or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Because of these risks, avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol (see **DRUG INTERACTIONS**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone.

Because of similar pharmacologic properties, it is reasonable to expect similar risk with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol.

Advise both patients and caregivers about the risks of respiratory depression and sedation if TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups are used with benzodiazepines, alcohol, or other CNS depressants.

There have been rare cases of posterior reversible encephalopathy (PRES)/reversible cerebral vasoconstriction syndrome (RCVS) reported with sympathomimetic drugs, including pseudoephedrine. Symptoms reported included sudden onset of severe headache, nausea, vomiting, and visual disturbances. Most cases improved or resolved within a few days following appropriate treatment. Pseudoephedrine should be discontinued immediately and medical advice sought if signs/symptoms of PRES/RCVS develop.

Serotonin syndrome: TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT 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 serotonergic 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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT 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**).

Psychomotor Impairment

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

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT may impair performance in tests of auditory vigilance. There is individual variation in response to antihistamines. Codeine may cause drowsiness or dizziness. The anticholinergic properties of triprolidine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.

Respiratory
Codeine, including TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups, 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.

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.

Ultra-Rapid Metabolizers of Codeine
Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may 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, Japanese and 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.

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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups, as in these patients, even usual therapeutic doses of TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups may decrease respiratory drive to the point of apnea. The use of TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

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-Market Adverse Drug Reactions**).

Special Populations

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

Pregnant Women: Studies in humans have not been conducted. While animal reproduction studies have revealed no evidence of harm to the fetus due to triprolidine/pseudoephedrine/codeine (see **TOXICOLOGY**), there is insufficient information available to determine the effects of guaifenesin. Combination products of Triprolidine hydrochloride-Pseudoephedrine hydrochloride- Codeine

phosphate and Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Guaifenesin-Codeine phosphate do cross the placental barrier. Thus, TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT are 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, can be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-marketing Experience**).

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Guaifenesin-Codeine phosphate are contraindicated during labour and delivery or in nursing mothers. Administration of opioids during labour may produce gastric stasis and increase the risk of vomiting and aspiration pneumonia in the mother. Life-threatening respiratory depression can occur in the infant if opioids are administered during labour. Naloxone, a drug that counters the effects of opiates, should be readily available if TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT are used in this population.

No clinical data on exposed pregnancies are available for Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Guaifenesin-Codeine phosphate. Animal studies with pseudoephedrine and triprolidine do not indicate direct or indirect harmful effects on embryofetal development (see **TOXICOLOGY** section). There is insufficient information available to determine the effects of guaifenesin.

Use in Lactation

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 (**see **WARNINGS AND PRECAUTIONS, 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. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. 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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT are contraindicated in breastfeeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breastfeeding.

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. The elderly may be more susceptible to adverse effects and are more likely to experience neurological anticholinergic effects and paradoxical excitation (see **DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age): TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups must not be used in patients under 18 years of age (see **CONTRAINDICATIONS**).

In young children, the respiratory centre is especially susceptible to the depressant action of opioid cough suppressants. Furthermore, codeine products (including TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to variable and unpredictable metabolism of codeine to morphine (see **CONTRAINDICATIONS, Ultra-Rapid Metabolizers of Codeine**).

Patients with Hepatic Impairment:
Experience with the use of the product suggests that normal adult dosage is appropriate in the presence of mild to moderate hepatic impairment, although it may be prudent to exercise caution (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **ACTION AND CLINICAL PHARMACOLOGY**).

There have been no specific studies of triprolidine, pseudoephedrine, codeine, or guaifenesin in hepatic impairment.

Patients with Renal Impairment:
Caution should be exercised when administering TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT products to patients with mild renal impairment, particularly if accompanied by cardiovascular disease (see **CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION,** and **ACTION AND CLINICAL PHARMACOLOGY**).

There have been no specific studies of triprolidine, codeine, or guaifenesin in renally impaired patients.

Laboratory Tests
If urine is collected within 24 hours of a dose of TEVA-COTRIDIN EXPECTORANT, a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

ADVERSE REACTIONS

Adverse Drug Reaction Overview
In some patients, nervousness, insomnia, sedation, drowsiness, dizziness, disturbance in attention, abnormal coordination, dry mouth, nose and throat, nausea, and vomiting may occur.

Triprolidine
Triprolidine may cause sedation, drowsiness, dizziness, disturbance in attention and abnormal coordination. Skin rashes, with or without irritation, have occasionally been reported. Dryness of the mouth, nose and throat may occur. Tachycardia, paradoxical excitation*, confusion**, nightmares***, hallucinations***, blurred vision, thickening of bronchial secretions, urinary retention, rash, urticaria and gastrointestinal disturbance including nausea and vomiting may also occur.

* Children and the elderly are more susceptible to paradoxical excitation (e.g. increased energy, restlessness, nervousness).
** The elderly are more prone to confusion.
*** Hallucinations and nightmares have been reported mainly in children.

Pseudoephedrine
Symptoms of central nervous system excitation may occur, including nervousness, agitation, restlessness, sleep disturbance, dizziness, and rarely, hallucinations. Dryness of the mouth, nausea, and vomiting may occur. Skin rashes, with or without irritation, have occasionally been reported with pseudoephedrine. Urinary retention has been reported occasionally in men receiving pseudoephedrine; prostatic enlargement could have been an important predisposing factor. Dysuria, increased blood pressure (not clinically significant at therapeutic doses), allergic dermatitis (a variety of allergic skin reactions, with or without systemic features such as bronchospasm, angioedema have been reported following use of pseudoephedrine), tachycardia and palpitations may also occur.

Codeine
In some patients, dizziness, worsening of headache with prolonged use, drowsiness, pruritus and sweating may occur.

In therapeutic doses, codeine is less likely than morphine to produce adverse effects. The most common adverse effects noted with codeine include nausea, vomiting, dyspepsia, and constipation. Micturition may be difficult. Dry mouth, vertigo, light-headedness, tachycardia, rash and urticaria also occur. These effects occur more commonly in ambulant patients than those at rest in bed. Therapeutic doses of codeine occasionally induce hallucinations. Acute pancreatitis in patients with a history of cholecystectomy and symptoms of central nervous system depression may also occur.

Guaifenesin
Gastrointestinal discomfort has occasionally been reported with guaifenesin. Allergic reactions, angioedema, anaphylactic reactions, rash, urticaria, dyspnoea, nausea, vomiting and abdominal discomfort may also occur.

Post-Marketing Experience
Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitarygonadal 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

Overview
TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should not be used with other cough and cold medications with an antihistamine, sympathomimetic, and antitussive.

Because of its pseudoephedrine content, combination products of Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Codeine phosphate and Triprolidine hydrochloride-Pseudoephedrine

hydrochloride-Guaifenesin-Codeine phosphate may interact with drugs acting on the cardiovascular system, including bretylium, guanethidine, methyldopa, and alpha- and beta- adrenergic blocking agents.

Concomitant administration of pseudoephedrine hydrochloride and MAOIs (or within two weeks of stopping an MAOI) may lead to hypertensive crisis. The anticholinergic effects of triprolidine are intensified by MAOIs (see **CONTRAINDICATIONS**).

Opiate analgesics may interact with monoamine oxidase inhibitors (MAOI) and result in serotonin syndrome (see **CONTRAINDICATIONS**).

Concomitant use of combination products of Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Codeine phosphate and Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Guaifenesin-Codeine phosphate with tricyclic antidepressants, triptans, or with sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like psychostimulants), which interfere with the catabolism of sympathomimetic amines, may cause a rise in blood pressure.

Codeine, like other opioids, may antagonise the effects of metoclopramide and domperidone on gastrointestinal motility.

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants (including alcohol): 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) increases the risk of respiratory depression, profound sedation, coma, and death and should be avoided (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

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

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

Drug-Laboratory Interactions
Codeine may increase serum amylase levels.

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

DOSAGE AND ADMINISTRATION

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should not be administered for more than 3 days. The maximum recommended daily dose of TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups is 40 mL (12 morphine milligram equivalent) for adults over the age of 18 years. Each patient should be assessed for their risk prior to prescribing TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups as the likelihood of experiencing serious adverse events can depend upon the type of opioid and duration of treatment, as well as the patient's own level of tolerance. In addition, the coughing should be assessed routinely to confirm the most appropriate dose and the need for further use of TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups.

Dosing Considerations

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should be avoided in patients known or suspected to be ultrarapid CYP2D6 metabolizers. Patients should be advised to seek medical advice if symptoms persist for more than 3 days. Do not increase the dose or the frequency of dosing.

Avoid use with other decongestants, anti-histamine-containing or other codeine containing products, including cough and cold medicines (see **WARNINGS AND PRECAUTIONS**).

Recommended Dose and Dosage Adjustment

Adults
Take 10 mL of syrup every 6-8 hours as required. Do not exceed 4 doses in a day (24 hours). Minimum time between doses: 6 hours.

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups are contraindicated in patients less than 18 years old.

Codeine, including TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed and not on scheduled intervals.

Patients with Hepatic Impairment:
Experience with the use of the product suggests that normal adult dosage is appropriate in the presence of mild to moderate hepatic impairment. TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups are contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**).

There have been no specific studies of triprolidine, pseudoephedrine, guaifenesin, or codeine in hepatic impairment.

Patients with Renal Impairment:

Caution should be exercised when administering TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups to patients with mild to moderate renal impairment, particularly if accompanied by cardiovascular disease (see **CONTRAINDICATIONS** section). TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups are contraindicated in patients with severe renal impairment (see **CONTRAINDICATIONS**).

There have been no specific studies of triprolidine, pseudoephedrine, guaifenesin, or codeine in renally impaired patients.

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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Although there have been no specific studies done on combination products of Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Codeine phosphate and Triprolidine hydrochloride-Pseudoephedrine hydrochloride-Guaifenesin-Codeine phosphate in this group of patients, it may be anticipated that the elderly may be more susceptible to adverse effects. Therefore, reduced dosage and careful monitoring is advised, particularly in cases where there is impairment of renal, hepatic or mental status (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

Adjustment or Reduction of Dosage:
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of prolonged 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.

Missed Dose
As there is no strictly scheduled dosing (see **Recommended Dose and Dosage Adjustment; Adults**), TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should be administered as needed for cough or to loosen phlegm and should not exceed 4 doses in a day (24 hours).

If the patient forgets to take one or more doses, they should ensure the next dose does not exceed the normal amount.

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

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups 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 lockable medication box could be obtained from a pharmacy.

OVERDOSAGE

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

Symptoms

In children, the ingredients, in overdosage, may produce hallucinations, convulsions and death. Symptoms of toxicity in children may include fixed dilated pupils, flushed face, dry mouth, fever, excitation, hallucinations, ataxia, incoordination, athetosis, tonic clonic convulsions, and postictal depression.

In addition to the undesirable effects seen with recommended doses, overdosage with codeine can cause transient euphoria, drowsiness, dizziness, weariness, diminution of sensibility, loss of sensation, vomiting, transient excitement in children and occasionally in adults, miosis progressing to nonreactive pinpoint pupils, itching sometimes with skin rashes and urticaria, and clammy skin with mottled cyanosis. In more severe cases, muscular relaxation with depressed or absent superficial and deep reflexes and a positive Babinski sign may appear. Marked slowing of the respiratory rate with inadequate pulmonary ventilation and consequent cyanosis may occur along with drowsiness, ataxia and, more rarely, pulmonary oedema, respiratory pauses, miosis, convulsion, collapse and urine retention. Terminal signs include shock, pulmonary edema, hypostatic or aspiration pneumonia and respiratory arrest, with death occurring within 6 to 12 hours following ingestion. Signs of histamine release have been observed.

Overdoses of antihistamines may cause hallucinations, convulsions or possibly death, especially in children. Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients. Overdosage with triprolidine is likely to result in effects similar to those listed under adverse reactions and may produce reactions varying from depression to stimulation of the CNS; the latter is particularly likely in children. Atropine-like signs and symptoms (dry mouth, fixed dilated pupils, flushing, tachycardia, hallucinations, convulsions, urinary retention, cardiac arrhythmias and coma) may occur. Additional symptoms may include ataxia, weakness, respiratory depression, dryness of the skin and mucous membranes, hyperpyrexia, tremor, psychosis, and convulsions.

Overdosage with pseudoephedrine can cause excessive CNS stimulation resulting in excitement, nervousness, anxiety, tremor, restlessness and insomnia. Other effects include tachycardia, hypertension, pallor, mydriasis, hyperglycemia and urinary retention. Severe overdosage may cause psychosis, tachypnea or hyperpnea, hallucinations, hypertensive crisis, convulsions or delirium, but in

some individuals there may be CNS depression with coma, somnolence, stupor or respiratory depression. Arrhythmias (including ventricular fibrillation) may lead to hypotension and circulatory collapse. Severe hypokalemia can occur, probably due to compartment shift rather than depletion of potassium. No organ damage or significant metabolic derangement is associated with pseudoephedrine overdosage.

Treatment
Therapy, if instituted within 4 hours of overdosage, is aimed at reducing further absorption of the drug. In the conscious patient, vomiting should be induced even though it may have occurred spontaneously. If vomiting cannot be induced, gastric lavage is indicated. Adequate precautions must be taken to protect against aspiration, especially in children. Charcoal slurry or other suitable agents should be instilled into the stomach after vomiting or lavage. Saline cathartics or milk of magnesia may be of additional benefit.

In the unconscious patient, the airway should be secured with a cuffed endotracheal tube before attempting to evacuate the gastric contents. Intensive supportive and nursing care is indicated, as for any comatose patient. If breathing is significantly impaired, maintenance of an adequate airway and mechanical support of respiration is the most effective means of providing adequate oxygenation.

Hypotension is an early sign of impending cardiovascular collapse and should be treated vigorously.

Do not use CNS stimulants. Convulsion should be controlled by careful administration of diazepam or short-acting barbiturate, repeated as necessary. Physostigmine may be also considered for use in controlling centrally-mediated convulsions.

Ice packs and cooling sponge baths, not alcohol, can aid in reducing the fever commonly seen in children.

For codeine, continuous stimulation that arouses, but does not exhaust, the patient is useful in preventing coma. Continuous or intermittent oxygen therapy is usually indicated, while naloxone is useful as a codeine antidote. Close nursing care is essential.

Saline cathartics, such as milk of magnesia, help to dilute the concentration of the drugs in the bowel by draining water into the gut, thereby hastening drug elimination.

Adrenergic receptor blocking agents are antidotes to pseudoephedrine. In practice, the most useful is the beta-blocker propranolol, which is indicated when there are signs of cardiac toxicity.

There are no specific antidotes to triprolidine. Histamine should not be given.

Pseudoephedrine and codeine are theoretically dialyzable, but the procedures have not been clinically established.

In severe cases of overdosage, it is essential to monitor both the heart by ECG and plasma electrolytes and to give i.v. potassium as indicated by these continuous controls. Vasopressors may be used to treat hypotension, and excessive CNS stimulation may be counteracted with parenteral diazepam. Stimulants should not be used.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Pseudoephedrine
Pseudoephedrine has direct and indirect sympathomimetic activity and is an effective upper respiratory decongestant. Pseudoephedrine is less potent than ephedrine in producing both tachycardia and elevation of systolic blood pressure and is also less potent in causing stimulation of the central nervous system. Pseudoephedrine produces its decongestant effect within 30 minutes, persisting for at least 4 hours.

Triprolidine
Triprolidine is a potent, competitive histamine H_1-receptor antagonist. Being an alkylamine, the drug possesses minimal anticholinergic activity. Triprolidine provides symptomatic relief in conditions believed to depend wholly, or partly, upon the triggered release of histamine. After oral administration of a single dose of 2.5 mg triprolidine to adults, the onset of action, as determined by the ability to antagonise histamine-induced wheals and flares in the skin, was within 1 to 2 hours. Peak effects occurred at about 3 hours, and although activity declined thereafter, significant inhibition of histamine-induced wheals and flares still occurred 8 hours after a single dose.

Codeine
Codeine is metabolized by the liver enzyme CYP2D6 into morphine, its active metabolite, which is an agonist of opiate receptors and possesses analgesic, antitussive, and antidiarrheal actions.

Guaifenesin
Guaifenesin is thought to exert its pharmacological action by stimulating receptors in the gastric mucosa. This increases the output from secretory glands of the gastrointestinal system and reflexly increases the flow of fluids from glands lining the respiratory tract. The result is an increase in volume and decrease in viscosity of bronchial secretions. Other actions may include stimulating vagal nerve endings in bronchial secretory glands and stimulating certain centres in the brain which in turn enhance respiratory fluid flow. Guaifenesin produces its expectorant action within 24 hours.

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

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

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

Gastrointestinal Tract and Other Smooth Muscle:

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

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

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

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

Pharmacokinetics
Absorption
Pseudoephedrine, triprolidine, guaifenesin, and codeine are well absorbed from the gut following oral administration.

Triprolidine and Pseudoephedrine
After the administration of 10 mL syrups (containing 2.5 mg triprolidine hydrochloride and 60 mg pseudoephedrine hydrochloride) to healthy adult volunteers,

- the peak plasma concentration (C_{max}) of triprolidine was 6.0 ng/mL, occurring at about 1.5 hours after drug administration

- the C_{max} of pseudoephedrine was approximately 180 ng/mL, with T_{max} occurring at approximately 1.5 hours after drug administration

Codeine
Following oral administration, peak plasma concentrations occur in approximately 1 hour. Maximum plasma concentrations of codeine are in the range of 100 to 300 ng/mL following normal therapeutic doses.

Guaifenesin
Guaifenesin is well absorbed from the gastrointestinal tract following oral administration, although limited information is available on its pharmacokinetics. After the administration of 600 mg guaifenesin to healthy volunteers, the C_{max} was approximately 1.4 micrograms/mL, with T_{max} occurring approximately 15 minutes after drug administration.

Distribution:
The apparent volumes of distribution (Vd/F) are approximately:

- 7.5 L/kg for triprolidine
- 2.8 L/kg for pseudoephedrine
- 3.6 L/kg for codeine

No information is available on the distribution of guaifenesin in humans.

Metabolism and Excretion:

Triprolidine
The plasma half-life (t½) of triprolidine was approximately 3.2 hours. Animal hepatic microsomal enzyme studies have revealed the presence of several triprolidine metabolites with an oxidized product of the toluene methyl group predominating. In man, it has been reported that only about 1% of an administered dose is eliminated as unchanged triprolidine over a 24-hour period. The apparent total body clearance of triprolidine (Cl/F) was approximately 30 to 37 mL/min/kg. The elimination rate constant (Kcl) was approximately 0.26 hr^{-1}.

Pseudoephedrine
The plasma half-life (t½) was approximately 5.5 hours. Pseudoephedrine is partly metabolized in the liver by N-demethylation to norpseudoephedrine, an active metabolite. Pseudoephedrine and its metabolite are excreted in the urine; 55% to 90% of a dose is excreted unchanged. The apparent total body clearance of pseudoephedrine (Cl/F) was approximately 7.5 mL/min/kg. The elimination rate constant (Kcl) was approximately 0.13 hr^{-1}. The rate of urinary elimination is accelerated when the urine is acidified. Conversely, as the urine pH increases, the rate of urinary excretion is slowed.

Codeine
The plasma half-life (t½) of codeine was approximately 3 to 4 hours.

Codeine is metabolized by the liver enzyme CYP2D6 via O-demethylation to form morphine, and via N-demethylation to form norcodeine. Codeine and its metabolites are also glucuronidated and sulphated in the liver.

Individuals who are heterozygous for the CYP2D6*2A allele are classified as ultra-rapid metabolizers of codeine. In these patients CYP2D6 enzyme is induced and O-demethylation of codeine to morphine is increased. If the patient is an extensive or ultra-rapid metabolizer, there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses (see **CONTRAINDICATIONS**).

After an oral dose, about 86% is excreted in the urine in 24 hours as free drug and metabolites, the majority as metabolites. Trace amounts of codeine are found in the feces. Unchanged drug accounts for 6 to 8% of the dose in urine in 24 hours, which may be increased to about 10% when the urinary pH is decreased.

Guaifenesin

Guaifenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaifenesin to 3 healthy male volunteers, the t½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

STORAGE AND STABILITY

TEVA-COTRIDIN Syrup: Protect from light. Store between 15°C-30°C.

TEVA-COTRIDIN EXPECTORANT Syrup: Protect from light. Store between 15°C-30°C. Do not refrigerate.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-COTRIDIN Syrup:
Each 5 mL of clear, dark red syrupy liquid with a sweet blackcurrant and pineapple flavour contains: triprolidine hydrochloride 2 mg, pseudoephedrine hydrochloride 30 mg and codeine phosphate 10 mg.

Non-medicinal ingredients in alphabetical order: Amaranth, artificial flavourings, glycerin, methylparaben, propylparaben, purified water, sorbitol solution and sucrose. Bottles of 100 mL and 2 L.

TEVA-COTRIDIN EXPECTORANT Syrup:
Each 5 mL of clear, orange syrupy liquid with a mixed fruit odour contains: triprolidine hydrochloride 2 mg, pseudoephedrine hydrochloride 30 mg, guaifenesin 100 mg and codeine phosphate 10 mg.

Non-medicinal ingredients in alphabetical order: Artificial flavourings, citric acid, FD&C yellow #6, maltitol solution, menthol, methylparaben, polyethylene glycol, propylene glycol, propylparaben, purified water, sodium citrate and sodium cyclamate.
Bottles of 500 mL and 2 L.

PART II: SCIENTIFIC INFORMATION

TOXICOLOGY

Mutagenicity
Triprolidine was not mutagenic in bacterial cells in an Ames test.

Pseudoephedrine is not genotoxic in a battery of *in vivo* and *in vitro* tests in bacterial and mammalian assay systems.

Codeine was not mutagenic in bacterial cells *in vitro*, or in an *in vivo* mouse micronucleus test.

There is insufficient information available to determine whether guaifenesin have genotoxic potential.

Carcinogenicity
Triprolidine and codeine were not carcinogenic in assays performed in mice and rats.

There is insufficient information available to determine whether pseudoephedrine or guaifenesin have carcinogenic potential.

Teratogenicity
Triprolidine did not produce teratogenic effects at oral doses of up to 125 mg/kg/day in the rat, or 100 mg/kg/day in the rabbit.

Pseudoephedrine did not produce teratogenic effects at oral doses of up to 432 mg/kg/day in the rat, or 200 mg/kg/day in the rabbit.

Codeine did not produce teratogenic effects at oral doses of up to 120 mg/kg/day in the rat, or 30 mg/kg/day in the rabbit. However, at 120 mg/kg/day there was an increase in mortality in rat embryos near the period of implantation.

Fertility
There is no information on the effect of triprolidine, pseudoephedrine, guaifenesin, or codeine on human fertility. Oral administration of pseudoephedrine to rats, at doses of 100 mg/kg/day in males and 20 mg/kg/day in females, did not impair fertility or alter morphological development and survival.

No studies have been conducted in animals to determine whether triprolidine or codeine have the potential to impair fertility.

There is insufficient information available to determine whether guaifenesin has the potential to impair fertility.

REFERENCE

1. Prescribing Information for [N]COVAN, by Pharmascience Inc., dated August 7, 2018, Control # 218014.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N]TEVA-COTRIDIN
(Triprolidine HCl – Pseudoephedrine HCl – Codeine phosphate)

[N]TEVA-COTRIDIN EXPECTORANT
(Triprolidine HCl – Pseudoephedrine HCl – Guaifenesin – Codeine phosphate)

Syrups

Read this carefully before you start taking TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups 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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups.

Serious Warnings and Precautions

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

- **You may get life-threatening breathing problems while taking TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT. 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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT. If a person has not been prescribed TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT, they could die from taking it. This is especially true for children.**

- **If you took TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT 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:**
  - **o has changes in their breathing (such as weak, difficult or fast breathing)**
  - **o is unusually difficult to comfort**
  - **o has tremors (shakiness)**
  - **o has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.

  Taking TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups 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 are TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups used for?
TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups are used for the temporary relief of coughs associated with allergies or the common cold. TEVA-COTRIDIN EXPECTORANT Syrup also loosens phlegm (mucus) to make coughs more productive. For adults 18 years or older.

How do TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups work?
Triprolidine is an antihistamine. Pseudoephedrine is a decongestant. Codeine acts on the brain to suppress cough. Guaifenesin is an expectorant.

What are the ingredients in TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups?
Medicinal ingredients:
Syrup: triprolidine hydrochloride, pseudoephedrine hydrochloride and codeine phosphate.
Expectorant Syrup: triprolidine hydrochloride, pseudoephedrine hydrochloride, guaifenesin and codeine phosphate.

Non-medicinal ingredients:
Syrup: Amaranth, artificial flavourings: currant and pineapple, glycerin, methylparaben, propylparaben, purified water, sorbitol solution and sucrose.
Expectorant Syrup: Artificial flavourings: coristex and currant, citric acid, FD&C yellow #6, maltitol solution, menthol, methylparaben, polyethylene glycol, propylene glycol, propylparaben, purified water, sodium citrate and sodium cyclamate.

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups come in the following dosage forms:
Syrup (2 mg triprolidine, 30 mg pseudoephedrine, 10 mg codeine in 5 mL of syrup): Bottles of 100 mL and 2 L.
Expectorant Syrup (2 mg triprolidine, 30 mg pseudoephedrine, 100 mg guaifenesin, 10 mg codeine in 5 mL of syrup): Bottles of 500 mL and 2 L.

Do not use TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups if you:

- did not receive a prescription from your doctor
- are under 18 years of age
- **pregnant, or in labour or delivery**
- are breastfeeding. The use of codeine-containing products while breastfeeding may harm your baby. If you breastfeed and take TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups, seek immediate medical care for your baby if they are overly drowsy, sedated, have difficulty breastfeeding, 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-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrup.
- have been told by your doctor that you break down codeine rapidly. This can lead to codeine overdose even at the usual adult dose.
- have a chronic cough that occurs with asthma, smoking or emphysema, or when there is an unusually large amount of mucus or phlegm with the cough.

- have a head injury or increased pressure in your head
- are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- have severe high blood pressure or heart condition
- have severe liver or kidney problems
- have pheochromocytoma (adrenal gland tumour)
- have ulcerative colitis
- you have severe pain in your abdomen
- are at risk for having seizures
- are allergic to this drug, other opioids or other antihistamines, to parabens (product contains methylparaben and propylparaben) or to any ingredient in the formulation (see "What are the ingredients in TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups?").
- have severe asthma, trouble breathing, bronchitis, emphysema or other breathing problems
- have bowel blockage or narrowing of the stomach or intestines
- suffer from alcoholism
- are taking medicines for cough and cold, Attention Deficit and Hyperactivity Disorder (ADHD) or to decrease appetite

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups. 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 high or low blood pressure, heart disease or a heart condition, liver or kidney problems, diabetes, glaucoma, thyroid disease, gallbladder disease including gallstones, enlarged prostate or difficulty in urinating, ulcers, bowel obstruction or abdominal pain or infections (such as an inflamed appendix or pancreas), or epilepsy
- suffer from migraines
- have severe kidney, liver or lung disease
- have chronic or severe constipation
- are older than 65 years old, or suffer from a long-term illness
- have asthma, a persistent or chronic cough or any other respiratory complications (i.e., difficulty breathing)
- are planning to become pregnant
- have or had depression
- are going to have, or recently had surgery
- are taking tranquilizers, sedatives, sedating antihistamines or other depressants
- are taking any other drug including over the counter drugs
- have diabetes, as TEVA-COTRIDIN Syrup contains sucrose
- have problems with your adrenal gland

Other warnings you should know about:
Accidentally taking TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrup can result in a fatal overdose. This is especially true if a child accidently takes it. Keep TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups out of sight and reach of children.

As with all opioids, taking TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrup may cause you to become dependent on it. Do not take more than the dose prescribed to you by your doctor.

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-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrup while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrup can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you took TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrup 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.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups. TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups can cause:

- drowsiness,
- dizziness, or
- lightheadedness

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

TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups are 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

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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups.

Serotonin Syndrome: TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups 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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups with certain antidepressants 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.

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 ultrarapid 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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups. Your healthcare professional should prescribe and administer TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups 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.

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-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups:

- other cough suppressants (antitussives) or decongestant medications
- antihistamines (drugs used to treat allergies)
- antidepressants (for depression and mood disorders) including St. John's Wort. Do not take TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat migraines (e.g. triptans)

- rarely, use of antidepressants or migraine medications with TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups may cause serotonin syndrome, changing how your brain, muscles and digestive system work. Symptoms include:
  o fever, sweating, shivering, diarrhea, nausea, vomiting;
  o muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
  o fast heartbeat, changes in blood pressure;
  o confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- medications for high blood pressure or heart conditions (like beta blockers)
- alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while you are taking TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrup. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- 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)
- other sedative drugs which may enhance the drowsiness caused by TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups
- domperidone and metoclopramide often used for nausea and vomiting and to help food move through digestion.
- anti-emetics (drugs used to prevent vomiting)
- drugs used to treat muscle spasms and back pain

How to take TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups:
Always take TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor should prescribe TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups at the lowest effective dose for the shortest period of time. It should only be used **as needed**. Do not take a dose unless you currently need it for cough or to loosen phlegm. Do not use for more than 3 days unless you are told to by your healthcare professional.

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

Usual Adult Dose:
Adults: 10 mL syrup/expectorant syrup three or four times a day. Wait at least 6 hours between doses. Do not exceed 4 doses in 24 hours.

Stopping your Medication

If you have been taking TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups for more than a few days you may experience some of the following uncomfortable symptoms when you stop taking it:

- 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 {added for consistency with ER wording}
- an unexplained fever
- weakness
- yawning

Overdose:

If you think you have taken too much TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups, 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
- feeling sick
- vomiting
- constipation
- decreased or lack of appetite.

Missed Dose:
As there is no scheduled dosing, take TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups as needed for cough or to loosen phlegm. Do not exceed 4 doses in 24 hours.

What are possible side effects from using TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups?
These are not all the possible side effects you may feel when taking TEVA-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- drowsiness
- headache
- dizziness
- problems with vision
- weakness, uncoordinated muscle movement
- vertigo
- lightheadedness, fainting
- difficulty sleeping, nightmares, disturbance in attention
- nervousness, agitation, restlessness, mild stimulation
- shortness of breath
- nausea, vomiting, or a poor appetite
- bloating
- dry mouth, nose and/or throat
- skin rash, itching or hives
- sweating
- constipation
- low sex drive, impotence (erectile dysfunction), infertility

Consult your doctor if you feel sedated or drowsy, confused, have shallow breathing or have severe constipation.

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	
COMMON			
Drowsiness		✓	
Depression: Feeling sad, unexplained weight change, sleep disturbances, lack of interest in usual activities, confused		✓	
Low Blood Pressure: Dizziness, fainting, lightheadedness		✓	
Difficult or painful urination, urine retention		✓	
Visions Changes: Blurred vision, glaucoma or other eye disorder		✓	
Thickening of secretions (phlegm) from the lungs		✓	
Inflammation of the Pancreas: Abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓	
RARE			
Encephalopathy (brain injury): Altered mental state, confusion, inability to concentrate, lethargy			✓
Cerebral Vasoconstriction Syndrome: Sudden, severe headache, nausea, vomiting, visual disturbances			✓
Codeine Overdose: Hallucinations, inability to walk normally, slow or weak breathing, extreme sleepiness, confusion, sedation, or dizziness, feeling sick, vomiting, constipation, decreased or lack of appetite, 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.		✓	
Ischemic Colitis: sudden abdominal pain, rectal bleeding or bloody stools			✓
Fast, Slow or Irregular Heartbeat: Heart		✓	

palpitations			
Low Blood Pressure: Dizziness, fainting, light-headedness	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

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

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **TEVA-COTRIDIN Syrup: Store between 15ºC and 30ºC. Protect from light.**
- **TEVA-COTRIDIN EXPECTORANT Syrup: Store between 15ºC and 30ºC. Protect from light. Do not refrigerate.**
- **Keep unused or expired TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups in a secure place to prevent theft, misuse or accidental exposure to children and pets.**
- **Keep TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups 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-COTRIDIN or TEVA-COTRIDIN EXPECTORANT Syrups, get emergency help right away.**

Disposal:
TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups should never be thrown into household trash, where children and pets may find it. It should be returned to pharmacy for proper disposal.

If you want more information about TEVA-COTRIDIN and TEVA-COTRIDIN EXPECTORANT Syrups:

- 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.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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