

Prescribing Information

^NCOACTIFED[®]

Syrup

(Triprolidine HCl – Pseudoephedrine HCl – Codeine phosphate)

Antihistamine – Antitussive Decongestant

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Prescribing Information

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(Triprolidine HCl – Pseudoephedrine HCl – Codeine Phosphate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	2 mg triprolidine, 30 mg pseudoephedrine, 10 mg codeine, in 5 mL of syrup.	Red colourant, flavour, glycerine, methylparaben, sodium benzoate, sucrose

INDICATIONS AND CLINICAL USE

Adults

COACTIFED[®] (triprolidine hydrochloride /pseudoephedrine hydrochloride/codeine phosphate) is 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 **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Pediatrics (< 18 years of age)

Regardless of the clinical setting, codeine, including COACTIFED[®] must not be used in patients below the age of 18 years due to increased safety concerns (see **CONTRAINDICATIONS**).

CONTRAINDICATIONS

COACTIFED[®] is contraindicated in:

- Patients under the age of 18 years.
- Women who are breastfeeding.
- Women who are pregnant or during labour and delivery.
- Patients who are known to be CYP2D6 extensive or ultra-rapid metabolisers 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; or to any ingredient in the formulation. COACTIFED[®] contains methylparaben. 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 (eg. 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 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

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.

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 COACTIFED[®] as it may increase the chance of experiencing serious adverse events, including death.

COACTIFED[®] 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.

COACTIFED[®] contains 3.0g of sucrose per 5 mL. COACTIFED[®] should be used with considerable caution in patients with diabetes mellitus.

COACTIFED[®] 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. COACTIFED[®] 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.

COACTIFED[®] 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, COACTIFED[®] is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, COACTIFED[®] should be prescribed and handled with caution.

Opioids, such as COACTIFED[®], should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse.

Carcinogenesis and Mutagenesis

See **TOXICOLOGY** section.

Cardiovascular

Codeine administration may result in hypotension and dizziness. COACTIFED[®] 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 COACTIFED[®] 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.

Gastrointestinal Effects

COACTIFED[®] 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 COACTIFED[®] as it 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. COACTIFED[®] 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 COACTIFED[®] is 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 COACTIFED[®], 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 COACTIFED[®] is 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.

Psychomotor Impairment

COACTIFED[®] 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.

COACTIFED[®] 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 COACTIFED[®], 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 COACTIFED[®], as in these patients, even usual therapeutic doses of COACTIFED[®] may decrease respiratory drive to the point of apnea. The use of COACTIFED[®] is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

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**), COACTIFED[®] does cross the placental barrier. Thus, COACTIFED[®] should not be administered to 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, COACTIFED[®] is contraindicated during labour 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. 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.

No clinical data on exposed pregnancies are available for COACTIFED[®]. Animal studies with pseudoephedrine and triprolidine do not indicate direct or indirect harmful effects on embryofetal development (see **TOXICOLOGY** section).

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). 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. 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 breast-feeding, 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, COACTIFED[®] is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating paediatricians about any use of codeine during breast-feeding.

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** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

Pediatrics (< 18 years of age): COACTIFED[®] 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, some children may be ultra-rapid metabolisers of codeine (see **CONTRAINDICATIONS, Ultra-Rapid Metabolisers 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 COACTIFED[®], triprolidine, pseudoephedrine or codeine in hepatic impairment.

Patients with Renal Impairment:

Caution should be exercised when administering COACTIFED[®] 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 COACTIFED[®], triprolidine or codeine in renally impaired patients.

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, pruritis 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.

DRUG INTERACTIONS

Overview

COACTIFED[®] should not be used with other cough and cold medications with an antihistamine, sympathomimetic, and antitussive.

Because of its pseudoephedrine content, COACTIFED[®] 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 COACTIFED[®] with tricyclic antidepressants, 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**). COACTIFED[®] should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

COACTIFED[®] 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 8 hours or every 6 hours. Do not exceed 4 doses in a day (24 hours).

COACTIFED[®] is contraindicated in patients less than 18 years old.

Codeine, including COACTIFED[®], 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. COACTIFED is contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**).

There have been no specific studies of COACTIFED[®], triprolidine, pseudoephedrine or codeine in hepatic impairment.

Patients with Renal Impairment:

Caution should be exercised when administering COACTIFED[®] to patients with mild to moderate renal impairment, particularly if accompanied by cardiovascular disease (see **CONTRAINDICATIONS** section). COACTIFED is contraindicated in patients with severe renal impairment (see **CONTRAINDICATIONS**).

There have been no specific studies of COACTIFED[®], triprolidine, pseudoephedrine 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. COACTIFED[®] 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 of COACTIFED[®] 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**).

Disposal

COACTIFED[®] should be kept in a safe place, out of the sight and reach of children before, during and after use. COACTIFED[®] should not be used in front of children, since they may copy these actions.

COACTIFED[®] should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired COACTIFED[®] should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets

Missed Dose

As there is no scheduled dosing, take COACTIFED[®] as needed for cough. Do not exceed 4 doses in a day (24 hours).

OVERDOSAGE

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

In children, the ingredients, in overdose, 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, overdose 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 dialysable, 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.

Tripolidine

Tripolidine is a potent, competitive histamine H₁-receptor antagonist. Being an alkylamine, the drug possesses minimal anticholinergic activity. Tripolidine 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 tripolidine 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 metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite, which is an agonist of opiate receptors and possesses analgesic, antitussive, and antidiarrheal actions.

Pharmacokinetics

Absorption:

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

Tripolidine and Pseudoephedrine

After the administration of 10 mL ACTIFED syrup (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.

Distribution:

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

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

Metabolism and Excretion:

Tripolidine

The plasma half-life ($t_{1/2}$) 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 (K_{el}) was approximately 0.26 hr^{-1} .

Pseudoephedrine

The plasma half-life ($t_{1/2}$) was approximately 5.5 hours. Pseudoephedrine is partly metabolised 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 (K_{el}) 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 ($t_{1/2}$) of codeine was approximately 3 to 4 hours.

Codeine is metabolised 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 metabolisers 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 metaboliser, 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.

STORAGE AND STABILITY

Store between 15°C and 30°C. Protect from light.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each 5 mL of clear, dark red syrupy liquid contains: triprolidine HCl 2 mg, pseudoephedrine HCl 30 mg and codeine phosphate 10 mg. Also contains methylparaben, sucrose, glycerine, sodium benzoate, red colourant and flavour. Alcohol-free. Bottles of 100 mL.

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.

Carcinogenicity

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

There is insufficient information available to determine whether pseudoephedrine has 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 COACTIFED[®] 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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^NCOACTIFED[®]

Syrup

(Triprolidine HCl – Pseudoephedrine HCl – Codeine phosphate)

Read this carefully before you start taking **COACTIFED[®]** 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 **COACTIFED[®]**.

Serious Warnings and Precautions

Taking COACTIFED[®] 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 COACTIFED[®] used for?

COACTIFED[®] is used for the temporary relief of cough associated with allergies or the common cold. For adults 18 years or older.

How does COACTIFED[®] work?

Triprolidine is an antihistamine. Pseudoephedrine is a decongestant. Codeine acts on the brain to suppress cough.

What are the ingredients in COACTIFED[®]?

Medicinal ingredients: Triprolidine hydrochloride, pseudoephedrine hydrochloride and codeine phosphate.

Non-medicinal ingredients: Flavour, glycerine, methylparaben, red colourant, sodium benzoate and sucrose. Alcohol-free.

COACTIFED[®] comes in the following dosage forms:

2 mg triprolidine, 30 mg pseudoephedrine, 10 mg codeine in 5 mL of syrup.

Do not use COACTIFED[®] if you:

- are under 18 years of age
- **are pregnant, or in labor or delivery**
- are breastfeeding. The use of codeine-containing products while breast-feeding may harm your baby.

If you breastfeed and take COACTIFED[®], 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 COACTIFED[®].

- 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
- are at risk for having seizures
- are allergic to this drug, other opioids or other antihistamines, to parabens (product contains methylparaben) or to any ingredient in the formulation (see "What are the ingredients in COACTIFED[®]?")
- 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 COACTIFED[®]. 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.
- 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 pregnant or planning to become pregnant.
- are breastfeeding
- have or had depression
- are taking tranquilizers, sedatives, sedating antihistamines or other depressants.
- are taking any other drug including over the counter drugs.
- have diabetes, as COACTIFED[®] contains sucrose.

Other warnings you should know about:

Accidentally taking COACTIFED[®] can result in a fatal overdose. This is especially true if a child accidentally takes it. Keep COACTIFED[®] out of sight and reach of children.

As with all opioids, taking COACTIFED[®] may cause you to become dependent on it. Do not take more than the dose prescribed to you by your doctor.

If you took COACTIFED[®] 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 COACTIFED[®]. COACTIFED[®] can cause:

- drowsiness
- dizziness or
- lightheadedness

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

COACTIFED[®] 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

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 COACTIFED[®]:

- other cough suppressants (antitussives) or decongestant medications
- antihistamines (drugs used to treat allergies)
- antidepressants (for depression and mood disorders). Do not take COACTIFED[®] 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)
- 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 COACTIFED[®]. 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)
- 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 COACTIFED[®]:

Always take COACTIFED[®] exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor should prescribe COACTIFED[®] 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. Do not use for more than 3 days unless you are told to by your healthcare professional.

Usual Adult dose:

Do not exceed 4 doses in 24 hours.

Adults: 10 mL syrup three or four times a day

Overdose:

If you think you have taken too much COACTIFED[®], 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 COACTIFED[®] as needed for cough. Do not exceed 4 doses in 24 hours.

What are possible side effects from using COACTIFED®?

These are not all the possible side effects you may feel when taking COACTIFED®. 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

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		✓	

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	
<p>Low Blood Pressure: dizziness, fainting, lightheadedness</p> <p>Difficult or painful urination, urine retention</p> <p>Visions Changes: blurred vision, glaucoma or other eye disorder</p> <p>Thickening of secretions (phlegm) from the lungs</p> <p>Inflammation of the Pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting</p>		✓	
		✓	
		✓	
		✓	
		✓	
<p>RARE</p> <p>Encephalopathy (brain injury) : altered mental state, confusion, inability to concentrate, lethargy</p> <p>Cerebral vasoconstriction syndrome: sudden, severe headache, Nausea, vomiting, visual disturbances</p> <p>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.</p> <p>Respiratory Depression: Slow, shallow or weak breathing.</p>			✓
			✓
			✓
			✓
			✓
<p>Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing</p> <p>Bowel Blockage (impaction): abdominal pain, severe constipation, nausea</p>			✓
			✓

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	
Ischemic colitis: sudden abdominal pain, rectal bleeding or bloody stools			✓
Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
Low Blood Pressure: dizziness, fainting, light-headedness.	✓		

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

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9
 Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep unused or expired COACTIFED[®] in a secure place to prevent theft, misuse or accidental exposure to children and pets.

Keep COACTIFED[®] out of sight and reach of children and pets.

Store between 15°C and 30°C. Protect from light.

Disposal:

COACTIFED[®] 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 COACTIFED[®]:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website; the manufacturer's website <http://www.gsk.ca>, or by contacting the sponsor;

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