PROMETHAZINE HYDROCHLORIDE AND CODEINE PHOSPHATE- promethazine hydrochloride and codeine phosphate solution
Tris Pharma Inc
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Promethazine Hydrochloride and Codeine Phosphate Oral Solution  CV

6.25 mg and 10 mg per 5 mL

Rx Only
BOXED WARNING

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF CODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; PROMETHAZINE AND RESPIRATORY DEPRESSION IN CHILDREN; MEDICATION ERRORS; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; NEONATAL OPIOID WITHDRAWAL SYNDROME

Addiction, Abuse, and Misuse

Promethazine HCl and Codeine Phosphate Oral Solution exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Reserve Promethazine HCl and Codeine Phosphate Oral Solution for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made. Assess each patient’s risk prior to prescribing Promethazine HCl and Codeine Phosphate Oral Solution, prescribe Promethazine HCl and Codeine Phosphate Oral Solution for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addition or abuse, and refill only after reevaluation of the need for continued treatment. (see WARNINGS)

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Promethazine HCl and Codeine Phosphate Oral Solution. Monitor for respiratory depression, especially during initiation of Promethazine HCl and Codeine Phosphate Oral Solution therapy or when used in patients at higher risk (see WARNINGS).

Accidental Ingestion

Accidental ingestion of even one dose of Promethazine HCl and Codeine Phosphate Oral Solution, especially by children, can result in a fatal overdose of codeine (see WARNINGS).

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism (see WARNINGS). Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. (see WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory Depression in Children).

Promethazine and Respiratory Depression in Children

Postmarketing cases of respiratory depression, including fatalities have been reported with use of promethazine in pediatric patients. Children may be particularly sensitive to the additive respiratory depressant effects when promethazine is combined with other respiratory depressants, including codeine. (see WARNINGS – Promethazine and Respiratory Depression in Children).
Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering Promethazine HCl and Codeine Phosphate Oral Solution. Dosing errors can result in accidental overdose and death. Always use an accurate milliliter measuring device when measuring and administering Promethazine HCl and Codeine Phosphate Oral Solution see (DOSAGE AND ADMINISTRATION, WARNINGS).

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex, requiring careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients who are taking a CYP3A4 inhibitor, CYP3A4 inducer, or 2D6 inhibitor (see PRECAUTIONS-Drug Interactions).

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS, PRECAUTIONS - Drug Interactions). Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients taking benzodiazepines, other CNS depressants, or alcohol. (see WARNINGS, PRECAUTIONS-Drug Interactions)

Neonatal Opioid Withdrawal Syndrome

Promethazine HCl and Codeine Phosphate Oral Solution is not recommended for use in pregnant women (see PRECAUTIONS - Pregnancy). Prolonged use of Promethazine HCl and Codeine Phosphate Oral Solution during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If Promethazine HCl and Codeine Phosphate Oral Solution is used for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see WARNINGS).

DESCRIPTION

Each 5 mL (one teaspoonful), for oral administration contains: Promethazine hydrochloride 6.25 mg; codeine phosphate 10 mg in a flavored syrup base with a pH between 4.8 and 5.4. Alcohol 8% (v/v).

Inactive Ingredients: anhydrous citric acid, ascorbic acid, D&C Red # 33, edetate disodium, FD&C Blue #1, methylparaben, peach-mint flavor, propylene glycol, propylparaben, purified water, saccharin sodium, sodium benzoate, sodium citrate anhydrous, sodium metabisulfite, sucrose.

Codeine is one of the naturally occurring phenanthrene alkaloids of opium derived from the opium poppy, it is classified pharmacologically as a narcotic analgesic. Codeine phosphate may be chemically designated as 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1)(salt) hemihydrate.

The phosphate salt of codeine occurs as white, needle-shaped crystals or white crystalline powder. Codeine phosphate is freely soluble in water and slightly soluble in alcohol. It has a molecular weight of 406.37, a molecular formula of C_{18}H_{21}NO_{3}•H_{3}PO_{4}•\frac{1}{2}H_{2}O, and the following structural formula:
Promethazine hydrochloride, a phenothiazine derivative, is chemically designated as (±)-10-[2-(Dimethylamino)propyl] phenothiazine monohydrochloride.

Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol. It has a molecular weight of 320.88, a molecular formula of C_{17}H_{20}N_{2}S•HCl, and the following structural formula:

\[\text{\includegraphics[width=0.5\textwidth]{promethamine.png}}\]

CLINICAL PHARMACOLOGY

Mechanism of Action

Codeine

Codeine sulfate is an opioid agonist relatively selective for the mu-opioid receptor, but with a much weaker affinity than morphine. The analgesic and antitussive properties of codeine have been speculated to come from its conversion to morphine. The precise mechanism of action of codeine and other opiates is not known; however, codeine is believed to act centrally on the cough center. In excessive doses, codeine will depress respiration.

Promethazine

Promethazine is a phenothiazine derivative, which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. Promethazine possesses antihistamine (H_{1} receptor antagonist), antiemetic, sedative, and anticholinergic effects. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.
**Pharmacodynamics**

**Codeine**

*Effects on the Central Nervous System*

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

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 origins may produce similar findings).

Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

*Effects on the 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

*Effects on the Cardiovascular System*

Codeine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

*Effects on the Endocrine System*

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans (see ADVERSE REACTIONS). They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date (see ADVERSE REACTIONS).

*Effects on the Immune System*

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

*Concentration–Adverse Reaction Relationships*

There is a relationship between increasing codeine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

**INDICATIONS AND USAGE**

Promethazine HCl and Codeine Phosphate Oral Solution is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold in patients 18 years of age
and older.

Important Limitations of Use:
- Not indicated for pediatric patients under 18 years of age (see PRECAUTIONS-Pediatric Use).
- Contraindicated in pediatric patients under 12 years of age (see CONTRAINDICATIONS, PRECAUTIONS-Pediatric Use).
- Contraindicated in pediatric patients 12 to 18 years of age after tonsillectomy or adenoidectomy (see CONTRAINDICATIONS, PRECAUTIONS-Pediatric Use).
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses (see WARNINGS), reserve Promethazine HCl and Codeine Phosphate Oral Solution for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made.

CONTRAINDICATIONS

Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated for:
- All children younger than 12 years of age (see PRECAUTIONS-Pediatric Use).
- Postoperative pain management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see PRECAUTIONS-Pediatric Use).
- Promethazine HCl and Codeine Phosphate Oral Solution is also contraindicated in patients with:
  - Significant respiratory depression (see WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory Depression).
  - Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (see WARNINGS).
  - Known or suspected gastrointestinal obstruction, including paralytic ileus (see WARNINGS).
  - A history of an idiosyncratic reaction to promethazine or to other phenothiazines (see WARNINGS).
  - Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within 14 days (see WARNINGS, PRECAUTIONS-Drug Interactions).
  - Hypersensitivity to codeine, promethazine, phenylephrine, or any of the inactive ingredients in Promethazine HCl and Codeine Phosphate Oral Solution [see ADVERSE REACTIONS]. Persons known to be hypersensitive to certain other opioids may exhibit cross-reactivity to codeine.

Sulfite Sensitivity

Sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

WARNINGS

(see Boxed Warnings)

Addiction, Abuse, and Misuse

Promethazine HCl and Codeine Phosphate Oral Solution contains codeine, a Schedule V controlled substance. As an opioid, Promethazine HCl and Codeine Phosphate Oral Solution exposes users to the risks of addiction, abuse, and misuse (see DRUG ABUSE AND DEPENDENCE), which can lead to overdose and death (see OVERDOSE). Reserve Promethazine HCl and Codeine Phosphate Oral Solution for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been
made. Assess each patient’s risk prior to prescribing Promethazine HCl and Codeine Phosphate Oral Solution, prescribe Promethazine HCl and Codeine Phosphate Oral Solution for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addiction or abuse, and refill only after reevaluation of the need for continued treatment.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Promethazine HCl and Codeine Phosphate Oral Solution. Addiction can occur at recommended dosages and if the drug is misused or abused. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Promethazine HCl and Codeine Phosphate Oral Solution. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug (see PRECAUTIONS-Information for Patients). Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, including codeine, one of the active ingredients in Promethazine HCl and Codeine Phosphate Oral Solution. Codeine produces dose-related respiratory depression by directly acting on the brain stem respiratory center that controls respiratory rhythm and may produce irregular and periodic breathing. Codeine is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to an increased exposure to the active metabolite morphine (see WARNINGS). Promethazine exerts a depressant effect on the respiratory center that is independent of and additive to that of other respiratory depressants, including codeine (see WARNINGS). Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression includes discontinuation of Promethazine HCl and Codeine Phosphate Oral Solution, close observation, supportive measures, and use of opioid antagonists (e.g. naloxone), depending on the patient’s clinical status (see OVERDOSAGE). Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Promethazine HCl and Codeine Phosphate Oral Solution, the risk is greatest during the initiation of therapy, when Promethazine HCl and Codeine Phosphate Oral Solution is used concomitantly with other drugs that may cause respiratory depression (see WARNINGS), in patients with chronic pulmonary disease or decreased respiratory reserve, and in patients with altered pharmacokinetics or altered clearance (e.g. elderly, cachectic, or debilitated patients) (see WARNINGS).

To reduce the risk of respiratory depression, proper dosing of Promethazine HCl and Codeine Phosphate Oral Solution is essential (see DOSAGE AND ADMINISTRATION, WARNINGS). Monitor patients closely, especially within the first 24 to 72 hours of initiating therapy or when used in patients at higher risk.

Overdose of codeine in adults has been associated with fatal respiratory depression, and the use of codeine in children younger than 12 years of age has been associated with fatal respiratory depression when used as recommended (see WARNINGS). Accidental ingestion of even one dose of Promethazine HCl and Codeine Phosphate Oral Solution, especially by children, can result in respiratory depression and death.

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-threatening Respiratory Depression in Children
Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated in all children younger than 12 years of age (see CONTRAINDICATIONS).
- Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS).
- Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity; severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression (see PRECAUTIONS-Pediatric Use).
- Healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose (see WARNINGS, PRECAUTIONS, OVERDOSAGE).

Lactation
At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with Promethazine HCl and Codeine Phosphate Oral Solution. (see PRECAUTIONS – Nursing Mothers).

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). 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 have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing. (See OVERDOSAGE). Therefore, individuals who are ultra-rapid metabolizers should not use Promethazine HCl and Codeine Phosphate Oral Solution.

Promethazine and Respiratory Depression in Children

Children

Postmarketing cases of respiratory depression, including fatalities have been reported with use of promethazine in pediatric patients. Concomitant administration with other respiratory depressants may increase the risk of respiratory depression. Children may be particularly sensitive to the additive respiratory depressant effects when promethazine is combined with other respiratory depressants, including codeine. See WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory
Depression for limitations on the use of Promethazine HCl and Codeine Phosphate Oral Solution in children.

Excessively large dosages of antihistamines, including promethazine hydrochloride, in pediatric patients may cause sudden death (see OVERDOSAGE).

Concomitant Conditions and Other Risk Factors

Avoid use of promethazine in patients at risk for respiratory depression. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. (see WARNINGS -Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants).

Pulmonary Considerations

Unresponsive Cough

The dosage of Promethazine HCl and Codeine Phosphate Oral Solution should not be increased if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease (see DOSAGE AND ADMINISTRATION).

Asthma and Other Pulmonary Disease

The use of Promethazine HCl and Codeine Phosphate Oral Solution in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated (see CONTRAINDICATIONS).

Opioid analgesics and antitussives, including codeine, one of the active ingredients in Promethazine HCl and Codeine Phosphate Oral Solution, should not be used in patients with acute febrile illness associated with productive cough or in patients with chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient’s respiratory function.

Promethazine HCl and Codeine Phosphate Oral Solution-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of Promethazine HCl and Codeine Phosphate Oral Solution (see WARNINGS).

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients (see WARNINGS).

Because of the risk of respiratory depression, avoid the use of opioid antitussives, including Promethazine HCl and Codeine Phosphate Oral Solution in patients with compromised respiratory function, patients at risk of respiratory failure, and in elderly, cachectic, or debilitated patients. If Promethazine HCl and Codeine Phosphate Oral Solution is prescribed, monitor such patients closely, particularly when initiating Promethazine HCl and Codeine Phosphate Oral Solution and when Promethazine HCl and Codeine Phosphate Oral Solution is given concomitantly with other drugs that depress respiration (see WARNINGS).

Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. To reduce the risk of overdose and respiratory depression, ensure that the dose of Promethazine HCl and Codeine Phosphate Oral Solution is communicated clearly and dispensed accurately (see DOSAGE AND ADMINISTRATION).

Advise patients to always use an accurate milliliter measuring device when measuring and administering
Promethazine HCl and Codeine Phosphate Oral Solution. Inform patients that household teaspoon is not an accurate measuring device and such use could lead to overdosage and serious adverse reactions (see OVERDOSAGE). For prescriptions where a measuring device is not provided, a pharmacist can provide an appropriate calibrated measuring device and can provide instructions for measuring the correct dose.

Activities Requiring Mental Alertness: Risks of Driving and Operating Machinery

Codeine and promethazine, two of the active ingredients in Promethazine HCl and Codeine Phosphate Oral Solution, may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Advise patients to avoid engaging in hazardous tasks requiring mental alertness and motor coordination after ingestion of Promethazine HCl and Codeine Phosphate Oral Solution. Avoid concurrent use of Promethazine HCl and Codeine Phosphate Oral Solution with alcohol or other central nervous system depressants because additional impairment of central nervous system performance may occur (see WARNINGS).

Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Promethazine HCl and Codeine Phosphate Oral Solution requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

Cytochrome P450 3A4 Interaction

The concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution with all cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome P450 2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

The concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients who are taking a CYP3A4 inhibitor or CYP3A4 inducer. If concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution with inhibitors and inducers of CYP3A4 is necessary, monitor patients for signs and symptoms that may reflect opioid toxicity and opioid withdrawal (see PRECAUTIONS-Drug Interactions).

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in codeine plasma concentrations and a decrease in active metabolite morphine plasma concentration which could result in an analgesic efficacy reduction or symptoms of opioid withdrawal.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients who are taking a CYP2D6 inhibitor. If concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution with
inhibitors of CYP2D6 is necessary, monitor patients for signs and symptoms that may reflect opioid toxicity and opioid withdrawal (see PRECAUTIONS - Drug Interactions).

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids, including Promethazine HCl and Codeine Phosphate Oral Solution, 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 PRECAUTIONS - 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 Promethazine HCl and Codeine Phosphate Oral Solution is used with benzodiazepines, alcohol, or other CNS depressants (see PRECAUTIONS – Information for Patients).

Risks of Use in Patients with Gastrointestinal Conditions

Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus (see CONTRAINDICATIONS). The use of codeine in Promethazine HCl and Codeine Phosphate Oral Solution may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

The concurrent use of anticholinergics with Promethazine HCl and Codeine Phosphate Oral Solution may produce paralytic ileus (see PRECAUTIONS - Drug Interactions).

The codeine in Promethazine HCl and Codeine Phosphate Oral Solution may result in constipation or obstructive bowel disease, especially in patients with underlying intestinal motility disorders. Use with caution in patients with underlying intestinal motility disorders.

The codeine in Promethazine HCl and Codeine Phosphate Oral Solution may cause spasm of the sphincter of Oddi, resulting in an increase in biliary tract pressure. Opioids may cause increases in serum amylase (see WARNINGS). Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Administration of promethazine has been associated with reported cholestatic jaundice.

Risks of Use in Patients with Head Injury, Impaired Consciousness, Increased Intracranial Pressure, or Brain Tumors

Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients with head injury, intracranial lesions, or a pre-existing increase in intracranial pressure. In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Promethazine HCl and Codeine Phosphate Oral Solution may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Furthermore, opioids produce adverse reactions that may obscure the clinical course of patients with head injuries.

Risk of Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with promethazine HCl alone or in combination with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).
The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of promethazine HCl, antipsychotic drugs, if any, and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Since recurrences of NMS have been reported with phenothiazines, avoid use of Promethazine HCl and Codeine Phosphate Oral Solution in patients with a history consistent with NMS.

**Risk of Paradoxical Reactions, including Dystonias**

Promethazine HCl and Codeine Phosphate Oral Solution contains promethazine, a phenothiazine. Phenothiazines are associated with dystonic reactions, particularly in pediatric patients who have an acute illness associated with dehydration. Paradoxical reactions, including dystonia, hyperexcitability, and abnormal movements have been reported in patients following a single administration of promethazine. Discontinue Promethazine HCl and Codeine Phosphate Oral Solution if a paradoxical reaction occurs.

**Increased Risk of Seizures in Patients with Seizure Disorders**

The codeine and promethazine in Promethazine HCl and Codeine Phosphate Oral Solution may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Promethazine HCl and Codeine Phosphate Oral Solution therapy.

**Concurrent administration with Monoamine Oxidase Inhibitors (MAOIs)**

Concurrent use of Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such therapy (see **CONTRAINdications**). MAOIs may potentiate the effects of morphine, codeine’s active metabolite, including respiratory depression, coma, and confusion MAOIs (see **PRECAUTIONS-Drug Interactions**).

**CNS Depression and Other CNS Effects**

- **CNS Depression**
  Promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore avoid use of Promethazine HCl and Codeine Phosphate Oral Solution in patients on these medications. (See **PRECAUTIONS – Information for Patients and Drug Interactions**).

- **Convulsions**
  Convulsions have occurred with therapeutic doses and overdoses of promethazine hydrochloride in pediatric patients. Promethazine may lower seizure threshold. It should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

- **Dystonias**
  Promethazine is a phenothiazine. Phenothiazines are associated with dystonic reactions. In pediatric
patients who are acutely ill associated with dehydration, there is an increased susceptibility to
dystonias with the use of promethazine HCl.

- **Head Injury and Increased Intracranial Pressure**
  The respiratory depressant effects of narcotic analgesics and their capacity to elevate cerebrospinal
  fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions, or a
  preexisting increase in intracranial pressure. Narcotics may produce adverse reactions which may
  obscure the clinical course of patients with head injuries.

**Cardiovascular Effects**

- **Hypotension**
  Codeine may produce orthostatic hypotension in ambulatory patients.

**Bone-Marrow Depression**

Promethazine should be used with caution in patients with bone-marrow depression. Leukopenia and
agranulocytosis have been reported, usually when promethazine HCl has been used in association with
other known marrow-toxic agents.

**Severe Hypotension**

Promethazine HCl and Codeine Phosphate Oral Solution may cause severe hypotension including
orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose
ability to maintain blood pressure has already been compromised by a reduced blood volume or
concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics)
(see **PRECAUTIONS-Drug Interactions**). Monitor these patients for signs of hypotension after
initiating Promethazine HCl and Codeine Phosphate Oral Solution.

In patients with circulatory shock, Promethazine HCl and Codeine Phosphate Oral Solution may cause
vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Promethazine
HCl and Codeine Phosphate Oral Solution in patients with circulatory shock.

**Neonatal Opioid Withdrawal Syndrome**

Promethazine HCl and Codeine Phosphate Oral Solution is not recommended for use in pregnant
women. Prolonged use of Promethazine HCl and Codeine Phosphate Oral Solution during pregnancy
can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal
syndrome in adults, may be life-threatening if not recognized and treated, and requires management
according to protocols developed by neonatology experts. Observe newborns for signs of neonatal
opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a
prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate
treatment will be available. (see **PRECAUTIONS-Information for Patients**).

**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.

**Constipation**

Codeine may cause or aggravate constipation.
Other Considerations
Administration of promethazine has been associated with reported cholestatic jaundice.
Administration of codeine may be accomplished by histamine release and should be used with caution in atopic children.

PRECAUTIONS

General
Narcotic analgesics, including codeine, should be administered with caution and the initial dose reduced in patients with acute abdominal conditions, convulsive disorders, significant hepatic or renal impairment, fever, hypothyroidism, Addison’s disease, ulcerative colitis, prostatic hypertrophy, in patients with recent gastrointestinal or urinary tract surgery, and in the very young or elderly or debilitated patients.

Promethazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

Anticholinergic Effects
Drugs having anticholinergic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Information for Patients
Advise patients of the risks of respiratory depression and death with Promethazine HCl and Codeine Phosphate Oral Solution in children younger than 18 years of age. Advise patients that Promethazine HCl and Codeine Phosphate Oral Solution should not be used in children younger than 18 years of age or in a child younger than 12 to 18 years of age for treatment after tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 18 receiving Promethazine HCl and Codeine Phosphate Oral Solution to monitor for signs of respiratory depression. (See WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory Depression).

Advise women that breastfeeding is not recommended during treatment with Promethazine HCl and Codeine Phosphate Oral Solution. (See WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory Depression).

Promethazine and codeine may cause marked drowsiness or may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from promethazine and codeine therapy. Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

Inform patients and caregivers that potentially fatal additive effects may occur if Promethazine HCl and Codeine Phosphate Oral Solution is used with benzodiazepines or other CNS depressants, including alcohol. Because of this risk, patients should avoid concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution with benzodiazepines or other CNS depressants, including alcohol. (See WARNINGS - Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants).

Patients should be advised to measure Promethazine HCl and Codeine Phosphate Oral Solution with an accurate measuring device. A household teaspoon is not an accurate measuring device and could lead to overdosage, especially when a half a teaspoon is measured. A pharmacist can recommend an appropriate measuring device and can provide instructions for measuring the correct dose.

Patients should be advised to report any involuntary muscle movements.
Avoid prolonged exposure to the sun.

Codeine, like other narcotic analgesics, may produce orthostatic hypotension in some ambulatory patients. Patients should be cautioned accordingly.

**Drug Interactions**

No specific drug interaction studies have been conducted with Promethazine HCl and Codeine Phosphate Oral Solution.

**Inhibitors of CYP3A4**

The concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution with CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin),azole-antifungal agents (e.g. ketoconazole), or protease inhibitors (e.g., ritonavir), may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Promethazine HCl and Codeine Phosphate Oral Solution is achieved (see **PRECAUTIONS**). After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower codeine levels, greater norcodeine levels, and less metabolism via CYP2D6 with resultant lower morphine levels (see **CLINICAL PHARMACOLOGY**), resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to codeine.

Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution while taking a CYP3A4 inhibitor. If concomitant use is necessary, monitor patients for respiratory depression and sedation at frequent intervals.

**CYP3A4 Inducers**

The concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution and CYP3A4 inducers, such as rifampin, carbamazepine, or phenytoin, can result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels (see **CLINICAL PHARMACOLOGY**), resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence (see **PRECAUTIONS**). After stopping a CYP3A4 inducer, as the effects of the inducer decline, codeine plasma concentrations may increase with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels (see **CLINICAL PHARMACOLOGY**), which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients who are taking CYP3A4 inducers. If concomitant use of a CYP3A4 inducer is necessary, follow the patient for reduced efficacy.

**Inhibitors of CYP2D6**

Codeine is metabolized by CYP2D6 to form morphine. The concomitant use of Promethazine HCl and Codeine Phosphate Oral Solution and CYP2D6 inhibitors, such as paroxetine, fluoxetine, bupropion, or quinidine, can increase the plasma concentration of codeine, but can decrease the plasma concentration of active metabolite morphine, which could result in reduced efficacy (see **CLINICAL PHARMACOLOGY**).

After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease but the active metabolite morphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression (see **CLINICAL PHARMACOLOGY**).

Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients who are taking
inhibitors of CYP2D6.

**Benzodiazepines, and Other CNS Depressants**

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients who are taking benzodiazepines or other CNS depressants (see **WARNINGS**).

**Serotonergic Drugs**

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation. Discontinue Promethazine HCl and Codeine Phosphate Oral Solution if serotonin syndrome is suspected.

**MAOIs**

Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated in patients who are taking MAOIs (i.e., certain drugs used for depression, psychiatric or emotional conditions, or Parkinson’s disease) or have taken MAOIs within 14 days (see **CONTRAINDICATIONS**).

MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) (see **WARNINGS**).

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly.

**Muscle Relaxants**

Codeine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients taking muscle relaxants. If concomitant use is necessary, monitor patients for signs of respiratory depression that may be greater than otherwise expected.

**Diuretics**

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

**Anticholinergic Drugs**

The concomitant use of anticholinergic drugs with Promethazine HCl and Codeine Phosphate Oral Solution may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus (see **PRECAUTIONS**). Monitor patients for signs of urinary retention or reduced gastric motility when Promethazine HCl and Codeine Phosphate Oral Solution is used concomitantly with anticholinergic drugs.

Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, or constipation) may occur when anticholinergic drugs are administered with promethazine.

**Drug/Laboratory Test Interactions**

Because narcotic analgesics may increase biliary tract pressure with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after administration of a dose of Promethazine HCl and Codeine Phosphate Oral Solution.
The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:

**Pregnancy Tests:** Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

**Glucose Tolerance Test:** An increase in blood glucose has been reported in patients receiving promethazine.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term animal studies have not been performed to assess the carcinogenic potential of codeine or of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with these agents. Codeine has been reported to show no evidence of carcinogenicity or mutagenicity in a variety of test systems, including the micronucleus and sperm abnormality assays and the Salmonella assay. Promethazine was nonmutagenic in the Salmonella test system of Ames.

**Pregnancy**

**Teratogenic Effects**

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

There are no studies in humans, and the significance of these findings to humans, if any, is not known.

**Promethazine:** Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine HCl. These doses are from approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject depending upon the indication for which the drug is prescribed. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women.

Animal reproduction studies have not been conducted with the drug combination-promethazine and codeine. It is not known whether this drug combination can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Promethazine HCl and Codeine Phosphate Oral Solution should be given to a pregnant woman only if clearly needed.

Promethazine HCl and Codeine Phosphate Oral Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects**

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

Promethazine administered to a pregnant woman within two weeks of delivery may inhibit platelet aggregation in the newborn.

**Labor and Delivery**
Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE).

Limited data suggest that use of promethazine hydrochloride during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn.

The effect of promethazine and/or codeine on later growth and development of the newborn is unknown. See also Nonteratogenic Effects.

Nursing Mothers

Codeine and its active metabolite, morphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression, and death in infants exposed to codeine via breast milk. Women who are ultra-rapid metabolizers of codeine achieve higher than expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous in their breastfed infants. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent.

There is no information on the effects of the codeine on milk production. Because of the potential for serious adverse reactions, including excess sedation, respiratory depression, and death in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Promethazine HCl and Codeine Phosphate Oral Solution. (see WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory Depression).

If infants are exposed to Promethazine HCl and Codeine Phosphate Oral Solution through breast milk, they should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

It is not known whether promethazine is excreted in human milk.

Pediatric Use

Promethazine HCl and Codeine Phosphate Oral Solution is not indicated for use in patients younger than 18 years of age because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks for use of codeine in these patients.

Life-threatening respiratory depression and death have occurred in children who received codeine (see WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory Depression). In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine.

Life-threatening respiratory depression and death have also occurred in children who received promethazine (see WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory Depression).

Because of the risk of life-threatening respiratory depression and death:

- Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated in all children younger than age 12 years of age. (see CONTRAINDICATIONS).
- Promethazine HCl and Codeine Phosphate Oral Solution is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy. (see CONTRAINDICATIONS).
Avoid the use of Promethazine HCl and Codeine Phosphate Oral Solution in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression (see WARNINGS - Ultra-Rapid Metabolism of Codeine and Respiratory Depression).

Geriatric Use
Clinical studies have not been conducted with Promethazine HCl and Codeine Phosphate Oral Solution in geriatric populations.

Use caution when considering the use of Promethazine HCl and Codeine Phosphate Oral Solution in patients 65 years of age or older. Elderly patients may have increased sensitivity to codeine; greater frequency of decreased hepatic, renal, or cardiac function; or concomitant disease or other drug therapy (see WARNINGS Life-Threatening Respiratory Depression).

Respiratory depression is the chief risk for elderly patients treated with opioids, including Promethazine HCl and Codeine Phosphate Oral Solution.

Respiratory depression has occurred after large initial doses of opioids were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration (see WARNINGS Life-Threatening Respiratory Depression).

Renal Impairment
The pharmacokinetics of Promethazine HCl and Codeine Phosphate Oral Solution has not been characterized in patients with renal impairment.

Codeine pharmacokinetics may be altered in patients with renal failure. Clearance may be decreased and the metabolites may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Promethazine HCl and Codeine Phosphate Oral Solution should be used with caution in patients with severe impairment of renal function, and patients should be monitored closely for respiratory depression, sedation, and hypotension.

Hepatic Impairment
No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of Promethazine HCl and Codeine Phosphate Oral Solution in this patient population are unknown. Promethazine HCl and Codeine Phosphate Oral Solution should be used with caution in patients with severe impairment of hepatic function, and patients should be monitored closely for respiratory depression, sedation, and hypotension.

Promethazine should be used with caution in patients with impairment of liver function.

Codeine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, monitor these patients closely for respiratory depression, sedation, and hypotension.

ADVERSE REACTIONS

Codeine

Central Nervous System: CNS depression, particularly respiratory depression, and to a lesser extent circulatory depression; light-headedness, dizziness, sedation, euphoria, dysphoria, headache, transient hallucination, disorientation, visual disturbances, and convulsions.
Cardiovascular: Tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension (common to narcotic analgesics).

Gastrointestinal: Nausea, vomiting, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility; in patients with acute ulcerative colitis, toxic dilation has been reported.

Genitourinary: Oliguria, urinary retention; antidiuretic effect has been reported (common to narcotic analgesics).

Allergic: Infrequent pruritus, giant urticaria, angioneurotic edema, and laryngeal edema.

Other: Flushing of the face, sweating and pruritus (due to opiate-induced histamine release); weakness.

Promethazine

Central Nervous System: Drowsiness is the most prominent CNS effect of this drug. Sedation, somnolence, blurred vision, dizziness, confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion; lassitude, tinnitus, incoordination, fatigue, euphoria, nervousness, diplopia, insomnia, tremors, convulsive seizures, excitation, catatonic-like states, hysteria. Hallucinations have also been reported.

Cardiovascular: Increased or decreased blood pressure, tachycardia, bradycardia, faintness.

Dermatologic: Dermatitis, photosensitivity, urticaria.

Hematologic: Leukopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis.

Gastrointestinal: Dry mouth, nausea, vomiting, jaundice.

Respiratory: Asthma, nasal stuffiness, respiratory depression (potentially fatal) and apnea (potentially fatal) (see WARNINGS – Promethazine; Respiratory Depression).

Other: Angioneurotic edema. Neuroleptic malignant syndrome (potentially fatal) has also been reported (see WARNINGS – Promethazine; Neuroleptic Malignant Syndrome).

Paradoxical Reactions: Hyperexcitability and abnormal movements have been reported in patients following a single administration of promethazine HCl. Consideration should be given to the discontinuation of promethazine HCl and to the use of other drugs if these reactions occur. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

To report SUSPECTED ADVERSE REACTIONS, contact Tris Pharma, Inc., at (732) 940-0358 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Promethazine HCl and Codeine Phosphate Oral Solution is a Schedule V Controlled Substance.

Abuse

Codeine

Promethazine HCl and Codeine Phosphate Oral Solution contains codeine, a substance with a high potential for abuse similar to other opioids including morphine and codeine. Promethazine HCl and Codeine Phosphate Oral Solution can be abused and is subject to misuse, addiction, and criminal diversion (see WARNINGS).

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic and antitussive products carries the risk of addiction even under appropriate medical use.
Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Promethazine HCl and Codeine Phosphate Oral Solution, like other opioids, can be diverted for non-medical use into illicit channels of distribution.

Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

**Risks Specific to Abuse of Promethazine HCl and Codeine Phosphate Oral Solution**

Promethazine HCl and Codeine Phosphate Oral Solution is for oral use only. Abuse of Promethazine HCl and Codeine Phosphate Oral Solution poses a risk of overdose and death. The risk is increased with concurrent use of Promethazine HCl and Codeine Phosphate Oral Solution with alcohol and other central nervous system depressants (see WARNINGS).

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

**Dependence**

Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, Promethazine HCl and Codeine Phosphate Oral Solution should be prescribed and administered for the shortest duration that is consistent with individual patient treatment goals and patients should be reevaluated prior to refills (see DOSAGE AND ADMINISTRATION, WARNINGS).

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral opioid use, although some mild degree of physical dependence may develop after a few days of opioid therapy.

If Promethazine HCl and Codeine Phosphate Oral Solution is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia,
nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs (see PRECAUTIONS-Pregnancy).

**OVERDOSAGE**

**Codeine**

Acute overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, partial or complete airway obstruction, atypical snoring, hypotension, circulatory collapse, cardiac arrest, and death.

Codeine may cause 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 overdose situations (see CLINICAL PHARMACOLOGY).

**Promethazine**

Signs and symptoms of overdosage with promethazine range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, unconsciousness and sudden death. Other reported reactions include hyperreflexia, hypertonia, ataxia, athetosis and extensor-plantar reflexes (Babinski reflex).

Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

Atropine-like signs and symptoms (dry mouth, fixed dilated pupils, flushing tachycardia, hallucinations, gastrointestinal symptoms, convulsions, urinary retention, cardiac arrhythmias and coma) may be observed.

Impaired secretion from sweat glands following toxic doses of drugs with anticholinergic side effects may predispose to hyperthermia.

**Treatment**

Treatment of overdosage is driven by the overall clinical presentation, and consists of discontinuation of Promethazine HCl and Codeine Phosphate Oral Solution together with institution of appropriate therapy. Give primary attention to the reestablishment of adequate respiratory exchange through provision of a patent and protected airway and the institution of assisted or controlled ventilation. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques. Gastric emptying may be useful in removing unabsorbed drug.

The opioid antagonists, naloxone and nalmefene, are specific antidotes for respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to codeine overdose, administer an opioid antagonist. An antagonist should not be administered in the absence of clinically significant respiratory depression. Because the duration of opioid reversal is expected to be less than the duration of action of codeine in Promethazine HCl and Codeine Phosphate Oral Solution, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product’s prescribing information. The respiratory depressant effects of promethazine are not reversed by opioid antagonists, such as naloxone.

Because of the potential for promethazine to reverse epinephrine’s vasopressor effect, epinephrine
should NOT be used to treat hypotension associated with promethazine overdose.

Hemodialysis is not routinely used to enhance the elimination of codeine or promethazine from the body.

**DOSAGE AND ADMINISTRATION**

**Important Dosage and Administration Instructions**

Administer Promethazine HCl and Codeine Phosphate Oral Solution by the oral route only. Always use an accurate milliliter measuring device when administering Promethazine HCl and Codeine Phosphate Oral Solution to ensure that the dose is measured and administered accurately. A household teaspoon is not an accurate measuring device and could lead to overdosage (see PRECAUTIONS).

For prescriptions where a measuring device is not provided, a pharmacist can provide an appropriate measuring device and can provide instructions for measuring the correct dose. Do not overfill. Rinse the measuring device with water after each use.

Advise patients not to increase the dose or dosing frequency of Promethazine HCl and Codeine Phosphate Oral Solution because serious adverse events such as respiratory depression may occur with overdosage (see PRECAUTIONS, OVERDOSAGE). The dosage of Promethazine HCl and Codeine Phosphate Oral Solution should not be increased if cough fails to respond; an unresponsive cough should be reevaluated for possible underlying pathology (see DOSAGE AND ADMINISTRATION, PRECAUTIONS).

**Recommended Dosage**

*Adults 18 years of age and older*: 5 mL every 4 to 6 hours as needed, not to exceed 6 doses (30 mL) in 24 hours.

**Monitoring, Maintenance, and Discontinuation of Therapy**

Prescribe Promethazine HCl and Codeine Phosphate Oral Solution for the shortest duration that is consistent with individual patient treatment goals (see PRECAUTIONS).

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy (see WARNINGS).

Reevaluate patients with unresponsive cough in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease (see WARNINGS). If a patient requires a refill, reevaluate the cause of the cough and assess the need for continued treatment with Promethazine HCl and Codeine Phosphate Oral Solution, the relative incidence of adverse reactions, and the development of addiction, abuse, or misuse (see WARNINGS).

Do not abruptly discontinue Promethazine HCl and Codeine Phosphate Oral Solution in a physically-dependent patient (see DRUG ABUSE AND DEPENDENCE). When a patient who has been taking Promethazine HCl and Codeine Phosphate Oral Solution regularly and may be physically dependent no longer requires therapy with Promethazine HCl and Codeine Phosphate Oral Solution, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both.

**HOW SUPPLIED**

Promethazine HCl and Codeine Phosphate is supplied as a clear, purple red, peach-mint flavor syrup containing promethazine HCl 6.25 mg/5 mL, codeine phosphate 10 mg/5 mL and alcohol 8% (v/v). It is
available as follows:
Bottles of 8 fluid ounces (237 mL), NDC 27808-065-01.
Bottles of 16 fluid ounces (473 mL), NDC 27808-065-02.

Keep bottles tightly closed.

Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Protect from light.

Dispense in tight, light-resistant container (USP) with a child-resistant closure.

DEA Order Form Required

Manufactured by
Tris Pharma, Inc.
Monmouth Junction, NJ 08852

www.trispharma.com

LB8082

Rev. 07  03/2018

MEDICATION GUIDE

**Promethazine (proe METH a zeen) Hydrochloride and Codeine (KOE deen) Phosphate Oral Solution, C-V**

**What is the most important information I should know about Promethazine Hydrochloride and Codeine Phosphate Oral Solution?**

Promethazine Hydrochloride and Codeine Phosphate Oral Solution is not for children under 18 years of age.

Promethazine Hydrochloride and Codeine Phosphate Oral Solution can cause serious side effects, including:

- **Addiction, abuse and misuse.** Taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution or other medicines that contain an opioid can cause addiction, abuse, and misuse, which can lead to overdose and death. This can happen even if you take Promethazine Hydrochloride and Codeine Phosphate Oral Solution exactly as prescribed by your healthcare provider. Your risk of addiction, abuse, and misuse is increased if you or a family member has a history of drug or alcohol abuse or addiction, or mental health problems.
  - Do not share your Promethazine Hydrochloride and Codeine Phosphate Oral Solution with other people.
  - Keep Promethazine Hydrochloride and Codeine Phosphate Oral Solution in a safe place away from children.

- **Life-threatening breathing problems (respiratory depression).** Promethazine Hydrochloride and Codeine Phosphate Oral Solution can cause breathing problems (respiratory depression) that can happen at any time during treatment and can lead to death. Your risk of breathing problems is greatest when you first start taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution, are taking other medicines that can cause breathing problems, have certain lung problems, or are elderly or have certain other health problems. **Children are at higher risk for respiratory depression.** Breathing problems can happen even if you take Promethazine Hydrochloride and Codeine Phosphate Oral Solution exactly as prescribed by your healthcare provider.
  - Call your healthcare provider or get emergency medical help right away if anyone taking
Promethazine Hydrochloride and Codeine Phosphate Oral Solution, or your breastfeeding baby has any of the symptoms below
- increased sleepiness
- confusion
- difficulty breathing
- shallow breathing
- limpness

- Keep Promethazine Hydrochloride and Codeine Phosphate Oral Solution in a safe place away from children. Accidental use of even 1 dose of Promethazine Hydrochloride and Codeine Phosphate Oral Solution, especially by a child, is a medical emergency and can cause breathing problems (respiratory depression) which can lead to death. If a child accidentally takes Promethazine Hydrochloride and Codeine Phosphate Oral Solution, get emergency medical help right away.

- Overdose and death due to medicine dosing errors. Overdose and death can happen if you measure the wrong dose of Promethazine Hydrochloride and Codeine Phosphate Oral Solution. Always use an accurate milliliter (mL) measuring device to measure the correct amount of Promethazine Hydrochloride and Codeine Phosphate Oral Solution. Do not use a household teaspoon to measure your medicine. You may accidentally take too much. You can ask your pharmacist for the measuring device you should use and how to measure the correct dose.

- Breathing problems (respiratory depression) that can lead to death and opioid withdrawal can happen if you start taking or stop taking other medicines while taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution, including:
  - certain antibiotics
  - certain medicines to treat a fungal infection
  - certain medicines to treat Human Immunodeficiency Virus (HIV)-1 infection, Acquired Immune Deficiency Syndrome (AIDS), or Hepatitis C
  - rifampin
  - carbamazepine
  - phenytoin

- Severe drowsiness, breathing problems (respiratory depression), coma, and death can happen in adults and children who take Promethazine Hydrochloride and Codeine Phosphate Oral Solution with benzodiazepines, or other central nervous system depressants, including alcohol.
  - Do not take any benzodiazepines or medicines that can cause drowsiness or sleepiness during treatment with Promethazine Hydrochloride and Codeine Phosphate Oral Solution. Ask your healthcare provider for a list of these medicines if you are not sure.
  - Do not drink alcohol during treatment with Promethazine Hydrochloride and Codeine Phosphate Oral Solution.

- Opioid withdrawal in a newborn. Use of Promethazine Hydrochloride and Codeine Phosphate Oral Solution during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. You should not take Promethazine Hydrochloride and Codeine Phosphate Oral Solution if you are pregnant. Tell your healthcare provider right away if you are pregnant or think you may be pregnant.

What is Promethazine Hydrochloride and Codeine Phosphate Oral Solution?
- Promethazine Hydrochloride and Codeine Phosphate Oral Solution is a prescription medicine used in adults to temporarily treat cough and upper respiratory symptoms that you can have with allergies or a common cold. Promethazine Hydrochloride and Codeine Phosphate Oral Solution contains 2 medicines, promethazine and codeine. Promethazine is an antihistamine. Codeine is an opioid (narcotic) cough suppressant.
- Promethazine Hydrochloride and Codeine Phosphate Oral Solution is a federal controlled substance (C-V) because it contains codeine that can be abused or lead to dependence. Keep
Promethazine Hydrochloride and Codeine Phosphate Oral Solution in a safe place to prevent misuse and abuse. Selling or giving away Promethazine Hydrochloride and Codeine Phosphate Oral Solution may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

Who should not take Promethazine Hydrochloride and Codeine Phosphate Oral Solution?

- Do not give Promethazine Hydrochloride and Codeine Phosphate Oral Solution to children younger than 12 years of age.
- Do not give Promethazine Hydrochloride and Codeine Phosphate Oral Solution to children younger than 18 years of age after tonsillectomy or adenoidectomy surgery.
- Do not take Promethazine Hydrochloride and Codeine Phosphate Oral Solution if you are allergic to any of the ingredients in Promethazine Hydrochloride and Codeine Phosphate Oral Solution. See the end of this Medication Guide for a complete list of ingredients in Promethazine Hydrochloride and Codeine Phosphate Oral Solution.
- Do not take Promethazine Hydrochloride and Codeine Phosphate Oral Solution if you have asthma.

Who should not take Promethazine Hydrochloride and Codeine Phosphate Oral Solution? Promethazine Hydrochloride and Codeine Phosphate Oral Solution is not for children under 18 years of age. See “What is the most important information I should know about Promethazine Hydrochloride and Codeine Phosphate Oral Solution?”

Do not take Promethazine Hydrochloride and Codeine Phosphate Oral Solution if you:

- have severe breathing problems (respiratory depression). See “What is the most important information I should know about Promethazine Hydrochloride and Codeine Phosphate Oral Solution?”
- have a blockage (obstruction) in your bowel such as a paralytic ileus.
- take a medicine called a monoamine oxidase inhibitor (MAOI).

- Do not take an MAOI within 14 days after you stop taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution.
- Do not start taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution if you stopped taking an MAOI in the last 14 days.

- have a type of glaucoma called “narrow angle glaucoma”.
- have problems with your urinary tract or difficulty urinating (urinary retention).
- are allergic to promethazine, codeine, or any of the ingredients in Promethazine Hydrochloride and Codeine Phosphate Oral Solution. See the end of this Medication Guide for a complete list of ingredients in Promethazine Hydrochloride and Codeine Phosphate Oral Solution. You may have an increased risk of an allergic reaction to Promethazine Hydrochloride and Codeine Phosphate Oral Solution if you are allergic to certain other opioid medicines. Ask your healthcare provider if you have any questions about this information.

Before you take Promethazine Hydrochloride and Codeine Phosphate Oral Solution, tell your healthcare provider about all of your medical conditions, including if you:

- have a drug addiction
- have lung or breathing problems
- have a fever and are coughing up mucus
- have had a recent head injury
- have had brain tumor or other brain problems
- have or have had seizures
- have pain in your stomach-area (abdomen)
- have constipation or other bowel problems
- have bile duct or pancreas problems
• have kidney or liver problems
• have prostate problems
• plan to have surgery
• have problems with your urinary tract or difficulty urinating
• have uncontrolled spasms of your face, neck or muscles of your body, arms and legs (dystonia)
• have a history of neuroleptic malignant syndrome (NMS)
• have blood disorders including low white blood cells
• have low blood pressure (hypotension)
• have adrenal gland problems
• are pregnant or plan to become pregnant. Promethazine Hydrochloride and Codeine Phosphate Oral Solution can harm your unborn baby. See “What is the most important information I should know about Promethazine Hydrochloride and Codeine Phosphate Oral Solution?”
• are breastfeeding or plan to breastfeed. Codeine Phosphate passes into your breast milk and can cause serious side effects in your baby including increased sleepiness, breathing problems (respiratory depression), and death. It is not known if Promethazine Hydrochloride can pass into your breast milk. You and your healthcare provider should decide if you will take Promethazine Hydrochloride and Codeine Phosphate Oral Solution or breastfeed. You should not do both. See “What should I avoid while taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution?”
• plan to have children. Promethazine Hydrochloride and Codeine Phosphate Oral Solution may affect the ability to have a child in females and males (fertility problems). It is not known if these fertility problems will be reversible, even after you stop taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution.
• Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution with certain other medicines can cause side effects or affect how well Promethazine Hydrochloride and Codeine Phosphate Oral Solution or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.
• Especially tell your healthcare provider if you:
  • See “What is the most important information I should know about Promethazine Hydrochloride and Codeine Phosphate Oral Solution?”
  • take pain medicines such as opioids (narcotics).
  • take cold or allergy medicines that contain antihistamines or cough suppressants.
  • drink alcohol.
  • take muscle relaxants.
  • take certain medicines used to treat mood, anxiety, psychotic or thought disorders, or depression, including monoamine oxidase inhibitors (MAOIs), tricyclics, selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), or antipsychotics.
  • take water pills (diuretics).
  • take medicines called “anticholinergics” used to treat asthma, chronic bronchitis (COPD), or stomach problems.

Ask your healthcare provider if you are not sure if you take one of these medicines.

How should I take Promethazine Hydrochloride and Codeine Phosphate Oral Solution?
• See “What is the most important information I should know about Promethazine Hydrochloride and Codeine Phosphate Oral Solution?”
• Take Promethazine Hydrochloride and Codeine Phosphate Oral Solution exactly as your healthcare provider tells you to take it. Do not change your dose without talking to your healthcare provider.
• Take Promethazine Hydrochloride and Codeine Phosphate Oral Solution by mouth only.
• **Do not** take more than 30 mL of Promethazine Hydrochloride and Codeine Phosphate Oral Solution in 24 hours.
• Take Promethazine Hydrochloride and Codeine Phosphate Oral Solution using an accurate millimeter (mL) measuring device. If you do not have one, ask your pharmacist to give you a measuring device to measure the correct amount of Promethazine Hydrochloride and Codeine Phosphate Oral Solution. **Do not use a household teaspoon to measure your medicine. You may accidently take too much.**
• Do not overfill the measuring device.
• Rinse your measuring device with water after each use.
• If you take too much Promethazine Hydrochloride and Codeine Phosphate Oral Solution, call your healthcare provider or go to the nearest hospital emergency room right away.
• Tell your healthcare provider if your cough does not get better within 5 days of treatment with Promethazine Hydrochloride and Codeine Phosphate Oral Solution.

**What should I avoid while taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution?**
• Avoid driving a car or operating machinery during treatment with Promethazine Hydrochloride and Codeine Phosphate Oral Solution. Promethazine Hydrochloride and Codeine Phosphate Oral Solution can cause you to be drowsy, slow your thinking and motor skills, and affect your vision.
• **Do not** drink alcohol during treatment with Promethazine Hydrochloride and Codeine Phosphate Oral Solution. Drinking alcohol with Promethazine Hydrochloride and Codeine Phosphate Oral Solution can increase your chances of having serious side effects, accidental overdose, and cause death.

**Avoid the use of Promethazine Hydrochloride and Codeine Phosphate Oral Solution if you:**
• are pregnant. Use of Promethazine Hydrochloride and Codeine Phosphate Oral Solution during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Tell your healthcare provider right away if you are pregnant or think you may be pregnant.
• are breastfeeding. Use of Promethazine Hydrochloride and Codeine Phosphate Oral Solution while breastfeeding can cause severe breathing problems (respiratory depression) that could be life-threatening.

**What are the possible side effects of Promethazine Hydrochloride and Codeine Phosphate Oral Solution?** Promethazine Hydrochloride and Codeine Phosphate Oral Solution may cause serious side effects, including:
• See “**What is the most important information I should know about Promethazine Hydrochloride and Codeine Phosphate Oral Solution?**”
• Bowel problems including constipation or stomach pain. See “**Who should not take Promethazine Hydrochloride and Codeine Phosphate Oral Solution?**”
• **Increased pressure in your head (increased intracranial pressure).** Avoid the use of Promethazine Hydrochloride and Codeine Phosphate Oral Solution if you have a head injury or have been told that you have changes in the tissue of your brain (brain lesions) or increased pressure in your head.
• **Neuroleptic malignant syndrome (NMS) which can lead to death.** Tell you healthcare provider right away if you have any of the following symptoms of NMS:
  - high fever
  - stiff muscles
  - confusion
  - sweating
  - changes in pulse, heart rate, or blood pressure
• **Uncontrolled spasms of your face and neck muscles, or muscles of your body, arms, and legs (dystonia).** These muscle spasms can cause abnormal movements and body positions, and speech problems. These spasms may happen after one dose of Promethazine Hydrochloride and Codeine Phosphate Oral Solution. Tell your healthcare provider if you have any of these symptoms.

• **Increased risk of seizures in people with seizure disorders.** If you have a seizure disorder, Promethazine Hydrochloride and Codeine Phosphate Oral Solution may increase how often you have seizures.

• **Low blood pressure.** A sudden drop in blood pressure can happen in some people during treatment with Promethazine Hydrochloride and Codeine Phosphate Oral Solution and this may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). Your risk of having this problem may be increased if you take Promethazine Hydrochloride and Codeine Phosphate Oral Solution with certain other medicines that lower blood pressure. If you have any of these symptoms while taking Promethazine Hydrochloride and Codeine Phosphate Oral Solution, sit or lie down. Do not change your body position too fast. Get up slowly from sitting or lying down.

• **Adrenal gland problems.** Promethazine Hydrochloride and Codeine Phosphate Oral Solution can cause serious and life-threatening adrenal gland problems. Your healthcare provider may do blood tests to check for adrenal gland problems. Call your healthcare provider right away if you have any of these symptoms:
  - nausea
  - vomiting
  - not wanting to eat
  - fatigue
  - weakness
  - dizziness
  - low blood pressure

• **Changes in laboratory blood levels,** including high blood sugar and false pregnancy test reading.

**The most common side effects of Promethazine Hydrochloride and Codeine Phosphate Oral Solution include:**

• sleepiness
• confusion
• coordination problems
• decrease in mental and physical performance
• lack of energy
• lightheadedness
• dizziness
• headache
• dry mouth
• irritability
• anxiety
• restlessness
• nervousness
• tremor
• difficulty urinating
• sweating
• shortness of breath
• nausea
• vomiting
• constipation

These are not all the possible side effects of Promethazine Hydrochloride and Codeine Phosphate Oral Solution. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Promethazine Hydrochloride and Codeine Phosphate Oral Solution?

• Store Promethazine Hydrochloride and Codeine Phosphate Oral Solution at room temperature between 68°F to 77°F (20°C to 25°C).
• Store Promethazine Hydrochloride and Codeine Phosphate Oral Solution in a tightly closed container, in a dry, cool place away from heat or direct sunlight.
• Keep Promethazine Hydrochloride and Codeine Phosphate Oral Solution and all medicines out of the reach of children.

How should I dispose of Promethazine Hydrochloride and Codeine Phosphate Oral Solution?
Remove unused Promethazine Hydrochloride and Codeine Phosphate Oral Solution from the container and mix it with an undesirable, non-toxic substance such as cat litter or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw it away in the household trash. You can also follow your state or local guidelines on how to safely throw away Promethazine Hydrochloride and Codeine Phosphate Oral Solution.

General information about the safe and effective use of Promethazine Hydrochloride and Codeine Phosphate Oral Solution.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Promethazine Hydrochloride and Codeine Phosphate Oral Solution for a condition for which it was not prescribed. Do not give Promethazine Hydrochloride and Codeine Phosphate Oral Solution to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about Promethazine Hydrochloride and Codeine Phosphate Oral Solution that is written for health professionals.

What are the ingredients in Promethazine Hydrochloride and Codeine Phosphate Oral Solution?
Active ingredients: promethazine hydrochloride and codeine phosphate
Inactive ingredients: anhydrous citric acid, ascorbic acid, D&C Red # 33, edetate disodium, FD&C Blue #1, methylparaben, peach-mint flavor, propylene glycol, propylparaben, purified water, saccharin sodium, sodium benzoate, sodium citrate anhydrous, sodium metabisulfite, sucrose.

Manufactured by:
Tris Pharma, Inc.
Monmouth Junction, NJ 08852
For more information, go to www.trispharma.com or call 1-732-940-0358.

LB8082
Rev. 07 03/2018

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approved: March 2018

PRINCIPAL DISPLAY PANEL
NDC 27808-065-02
Promethazine Hydrochloride and Codeine Phosphate Oral Solution CV
6.25 mg and 10 mg per 5 mL
Alcohol 8% (v/v)
WARNINGS: Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions.

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

15 fl. oz. (473 mL)
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**Packaging**

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**Marketing Information**

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**Labeler** - Tris Pharma Inc (947472119)