

CII ZUTRIPRO® Oral Solution

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZUTRIPRO Oral Solution safely and effectively. See full prescribing information for ZUTRIPRO Oral Solution.

ZUTRIPRO (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) Oral Solution.

Initial U.S. Approval: 2011

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.1), Drug Interactions (7.1)]. Avoid use of opioid cough medications in patients taking benzodiazepines, CNS depressants, or alcohol.

RECENT MAJOR CHANGES

Boxed Warning 1/2017
Warnings and Precautions (5) 1/2017

INDICATIONS AND USAGE

ZUTRIPRO Oral Solution is a combination product containing an antitussive, an antihistamine, and a nasal decongestant indicated for:

- Relief of cough and nasal congestion associated with common cold (1.1)
- Relief of symptoms including nasal congestion associated with upper respiratory allergies (1.2)

Important Limitations of Use:

Not indicated for pediatric patients under 18 years of age

DOSAGE AND ADMINISTRATION

For Oral Use Only

- Adults 18 years of age and older: 5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours. (2)

DOSAGE FORMS AND STRENGTHS

Each 5 mL of ZUTRIPRO Oral Solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg. (3)

CONTRAINDICATIONS

- Patients with known hypersensitivity to hydrocodone bitartrate, pseudoephedrine hydrochloride, chlorpheniramine, or any of the inactive ingredients of ZUTRIPRO. (4)
- Patients receiving monoamine oxidase inhibitor (MAOI) therapy or within 14 days of stopping such therapy. (4)
- Patients with narrow angle glaucoma, urinary retention, severe hypertension or severe coronary artery disease. (4)

WARNINGS AND PRECAUTIONS

- Risks from Concomitant Use with Benzodiazepines or other CNS Depressants: Use with caution. (5.1)
- Drug Dependence: Prescribe with caution that is appropriate to the use of other opioids. (5.3)
- Head injury and increased intracranial pressure: Avoid in patients with head injury, intra-cranial lesions, or increased intracranial pressure. (5.4)
- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring complete mental alertness such as driving or operating machinery. (5.5)
- Avoid concurrent use of alcohol or other central nervous system depressants. (5.5)
- Acute abdominal conditions: Use with caution in patients with acute abdominal conditions. (5.6)
- Coexisting conditions: Use with caution in patients with diabetes, thyroid disease, Addison's disease, prostatic hypertrophy or urethral stricture, or asthma. (5.11)

ADVERSE REACTIONS

The most common adverse reactions of ZUTRIPRO Oral Solution include: Sedation, somnolence, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, nervousness, or sleeplessness; blurred, double, or other visual disturbances; confusion, headache, euphoria, facial dyskinesia, feeling faint, lightheadedness, agitation, restlessness, insomnia, irritability, tremor. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Hawthorn Pharmaceuticals, Inc. at tel: 1-800-793-2145 and www.hawthornrx.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants: Avoid using with ZUTRIPRO; May cause additive CNS depression. (7.1)
- MAOIs or tricyclic antidepressants: Do not use. May increase the effect of either the antidepressant or hydrocodone; may cause increase in blood pressure or hypertensive crisis may occur. (7.2)
- Anticholinergic drugs: Use with caution. Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, or constipation) may occur (7.3)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Use with caution in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use with caution in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 1/2017

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CII

FULL PRESCRIBING INFORMATION

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.1), Drug Interactions (7.1)]. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.

1 INDICATIONS AND USAGE

1.1 Common Cold

ZUTRIPRO Oral Solution is indicated for relief of cough and nasal congestion associated with the common cold in adults 18 years of age and older.

1.2 Upper Respiratory Allergies

ZUTRIPRO Oral Solution is indicated for relief of symptoms including nasal congestion associated with upper respiratory allergies in adults 18 years of age and older.

Important Limitations of Use

Not indicated for pediatric patients under 18 years of age [see *Pediatric Use (8.4)*].

2 DOSAGE AND ADMINISTRATION

Administer ZUTRIPRO Oral Solution by the oral route only. Measure ZUTRIPRO Oral Solution with an accurate milliliter measuring device. Do not use a household teaspoon to measure the dose [see *Warnings and Precautions (5.10)*].

2.1 Adults 18 Years of Age and Older

5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

3 DOSAGE FORMS AND STRENGTHS

ZUTRIPRO is a clear, colorless to light yellow, grape-flavored liquid.

5 mL of ZUTRIPRO Oral Solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg [see *Description (11)*].

4 CONTRAINDICATIONS

ZUTRIPRO Oral Solution is contraindicated in:

- Patients with known hypersensitivity to hydrocodone bitartrate, pseudoephedrine hydrochloride, chlorpheniramine maleate, or any of the inactive ingredients of ZUTRIPRO Oral Solution.

- Patients receiving MAOI therapy or within 14 days of stopping such therapy.
- Patients with narrow angle glaucoma, urinary retention, severe hypertension, or severe coronary artery disease.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Concomitant use of opioids, including ZUTRIPRO, with benzodiazepines, or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Because of these risks, avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol [*see Drug Interactions (7.1)*].

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 ZUTRIPRO is used with benzodiazepines, alcohol, or other CNS depressants [*see Patient Counseling Information (17.3)*].

5.2 Respiratory Depression

Hydrocodone bitartrate, one of the active ingredients of ZUTRIPRO Oral Solution, produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Overdose of hydrocodone bitartrate in adults has been associated with fatal respiratory depression, and the use of hydrocodone bitartrate in children less than 6 years of age has been associated with fatal respiratory depression. Exercise caution when administering ZUTRIPRO Oral Solution because of the potential for respiratory depression. If respiratory depression occurs, discontinue ZUTRIPRO Oral Solution and use naloxone hydrochloride when indicated to antagonize the effect and other supportive measures as necessary [*see Overdosage (10)*].

5.3 Drug Dependence

Hydrocodone can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of ZUTRIPRO Oral Solution. Prescribe and administer ZUTRIPRO with the same degree of caution appropriate to the use of other opioid drugs [*see Drug Abuse and Dependence (9.2, 9.3)*].

5.4 Head Injury and Increased Intracranial Pressure

The respiratory depression effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries. The use of ZUTRIPRO Oral Solution should be avoided in these patients.

5.5 Activities Requiring Mental Alertness

Hydrocodone bitartrate and chlorpheniramine maleate, two of the active ingredients in ZUTRIPRO 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

ZUTRIPRO Oral Solution. Concurrent use of ZUTRIPRO Oral Solution with alcohol or other central nervous system depressants should be avoided because additional impairment of central nervous system performance may occur.

5.6 Acute Abdominal Conditions

ZUTRIPRO Oral Solution should be used with caution in patients with acute abdominal conditions since the administration of hydrocodone may obscure the diagnosis or clinical course of patients with acute abdominal conditions. The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus [*see Drug Interactions (7.3)*].

5.7 Co-administration with Anticholinergics

The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus. Exercise caution when using ZUTRIPRO Oral Solution in patients taking anticholinergic medications. [*see Drug Interactions (7.3)*].

5.8 Co-administration with MAOIs or Tricyclic Antidepressants

ZUTRIPRO Oral Solution should not be used in patients receiving MAOI therapy or within 14 days of stopping such therapy as an increase in blood pressure or hypertensive crisis, may occur. In addition, the use of MAOIs or tricyclic antidepressants with hydrocodone bitartrate, one of the active ingredients in ZUTRIPRO Oral Solution, may increase the effect of either the antidepressant or hydrocodone [*see Contraindications (4) and Drug Interactions (7.2)*].

5.9 Cardiovascular and Central Nervous System Effects

The pseudoephedrine hydrochloride contained in ZUTRIPRO Oral Solution can produce cardiovascular and central nervous system effects in some patients such as insomnia, dizziness, weakness, tremor, or arrhythmias. In addition, central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension has been reported. Therefore, ZUTRIPRO Oral Solution should be used with caution in patients with cardiovascular disorders, and should not be used in patients with severe hypertension or coronary artery disease.

5.10 Dosing

Patients should be advised to measure ZUTRIPRO Oral Solution with an accurate milliliter measuring device. Patients should be informed that a household teaspoon is not an accurate measuring device and could lead to overdosage, which can result in serious adverse reactions [*see Overdosage (10)*]. Patients should be advised to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose.

5.11 Coexisting Conditions

ZUTRIPRO Oral Solution should be used with caution in patients with diabetes, thyroid disease, Addison's disease, prostatic hypertrophy or urethral stricture, and asthma.

5.12 Renal Impairment

ZUTRIPRO Oral Solution should be used with caution in patients with severe renal impairment [*see Use in Specific Populations (8.6); Pharmacokinetics (12.3)*].

5.13 Hepatic Impairment

ZUTRIPRO Oral Solution should be used with caution in patients with severe hepatic impairment [*see Use in Specific Populations (8.7)*].

6 ADVERSE REACTIONS

Use of hydrocodone bitartrate, a semisynthetic opioid, may result in the following:

- Respiratory depression [*see Warnings and Precautions (5.2) and Overdosage (10)*]
- Drug dependence [*see Warnings and Precautions (5.3)*]
- Increased intracranial pressure [*see Warnings and Precautions (5.4) and Overdosage (10)*]
- Decreased mental alertness with impaired mental and/or physical abilities [*see Warnings and Precautions (5.5)*]
- Paralytic ileus [*see Warnings and Precautions (5.6)*]

Use of pseudoephedrine, a sympathomimetic amine, may result in the following:

- Central nervous system effects such as insomnia, dizziness, weakness, tremor, or convulsions [*see Warnings and Precautions (5.9)*]
- Cardiovascular system effects such as arrhythmias, or increased blood pressure, cardiovascular collapse with accompanying hypotension [*see Warnings and Precautions (5.9)*]

Use of chlorpheniramine, an antihistamine, may result in:

- Decreased mental alertness with impaired mental and/or physical abilities [*see Warnings and Precautions (5.5)*]

The most common adverse reactions of ZUTRIPRO Oral Solution include: Sedation, somnolence, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, nervousness, or sleeplessness; blurred, double, or other visual disturbances; confusion, headache, euphoria, facial dyskinesia, feeling faint, lightheadedness, agitation, restlessness, insomnia, irritability, tremor.

Other adverse reactions include:

Cardiovascular: Fast, or slow heartbeat, hypertension, hypotension, orthostatic hypotension, palpitations, shock-like state, syncope.

Respiratory: Dryness of the pharynx and respiratory passages, occasional tightness of the chest, laryngismus, wheezing, or troubled breathing.

Gastrointestinal System: Nausea and vomiting (more frequent in ambulatory than in recumbent patients), constipation, abdominal distension, abdominal pain, acute pancreatitis, dry mouth, dyspepsia, epigastric distress, and/or loss of appetite.

Genitourinary System: Ureteral spasm, spasm of vesicle sphincters, urinary retention, dysuria, urinary frequency, urinary hesitancy.

Dermatological System: Skin rash, pruritus, erythema, urticaria, excessive perspiration.

Endocrine System: Changes in glucose utilization, decreased lactation, early menses, glycosuria, gynecomastia, hypoglycemia, increased appetite, increased libido, pheochromocytoma stimulation.

Special Senses: labyrinthitis, tinnitus, vertigo, hypermetropia, lacrimation increased, mydriasis, photophobia.

7 DRUG INTERACTIONS

No specific interaction studies have been conducted with ZUTRIPRO Oral Solution.

7.1 Benzodiazepines, Opioids, Antihistamines, Antipsychotics, Anti-anxiety Agents, or Other CNS Depressants (Including Alcohol)

The use of benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants concomitantly with ZUTRIPRO Oral Solution may cause an additive CNS depressant effect, profound sedation, respiratory depression, coma, and death and should be avoided [*see Warnings and Precautions (5.1)*].

7.2 MAOIs and Tricyclic Antidepressants

Do not prescribe ZUTRIPRO Oral Solution if the patient is taking a prescription MAOI (i.e., certain drugs used for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping a MAOI drug. The use of MAOIs or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. An increase in blood pressure or hypertensive crisis may also occur when pseudoephedrine containing preparations are used with MAOIs [*see Warnings and Precautions (5.8)*].

7.3 Anticholinergic Drugs

Hydrocodone and chlorpheniramine should be administered cautiously to persons receiving other anticholinergic drugs in order to avoid paralytic ileus and excessive anticholinergic effects.

Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, or constipation) may occur when anticholinergic drugs are administered with chlorpheniramine [*see Warnings and Precautions (5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of ZUTRIPRO Oral Solution in pregnant women. Reproductive toxicity studies have not been conducted with ZUTRIPRO Oral Solution; however, studies are

available with individual active ingredients or related active ingredients. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. A single retrospective study reported that chlorpheniramine was teratogenic in humans; however, the significance of these findings was not known. Developmental toxicity was also evident with chlorpheniramine in mice and rats. Because animal reproduction studies are not always predictive of human response, ZUTRIPRO Oral Solution should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Hydrocodone:

Hydrocodone has been shown to be teratogenic in hamsters when given in a dose approximately 35 times the maximum recommended human daily dose (MRHDD) (on a mg/m^2 basis at a single subcutaneous dose of 102 mg/kg on gestation day 8). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In a study in which pregnant rats were dosed throughout organogenesis, a dose of codeine approximately 50 times the MRHDD of hydrocodone (on a mg/m^2 basis at an oral dose of 120 $\text{mg}/\text{kg}/\text{day}$ of codeine) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, doses of codeine up to approximately 25 and 120 times, respectively, the MRHDD of hydrocodone (on a mg/m^2 basis at oral doses of 30 and 600 $\text{mg}/\text{kg}/\text{day}$, respectively), produced no adverse developmental effects.

Chlorpheniramine:

A retrospective study found a small, but statistically significant, association between maternal use of chlorpheniramine and inguinal hernia and eye or ear anomalies in children. Other retrospective studies have found that the frequency of congenital anomalies, in general, was not increased among offspring of women who took chlorpheniramine during pregnancy. The significance of these findings to the therapeutic use of chlorpheniramine in human pregnancy is not known.

In studies with chlorpheniramine in which pregnant rats and rabbits were dosed throughout organogenesis, oral doses up to approximately 20 and 25 times the MRHDD on a mg/m^2 basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, a dose approximately 5 times the MRHDD (on a mg/m^2 basis at an oral dose of 20 $\text{mg}/\text{kg}/\text{day}$) was embryolethal, and postnatal survival was decreased when dosing was continued after parturition. Embryolethality was also observed when male and female rats were dosed with approximately 5 times the MRHDD (on a mg/m^2 basis at an oral dose of 10 $\text{mg}/\text{kg}/\text{day}$) prior to mating.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

8.2 Labor and Delivery

As with all opioids, administration of ZUTRIPRO Oral Solution to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

8.3 Nursing Mothers

Caution should be exercised when ZUTRIPRO is administered to nursing mothers. Hydrocodone, chlorpheniramine and pseudoephedrine are excreted in human milk. The clinical significance is unknown; however, the anticholinergic action of chlorpheniramine may suppress lactation if taken prior to nursing.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ZUTRIPRO Oral Solution, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of ZUTRIPRO Oral Solution in pediatric patients under 18 years of age have not been established. The use of hydrocodone in children less than 6 years of age has been associated with fatal respiratory depression [see *Warnings and Precautions (5.2)*].

8.5 Geriatric Use

Clinical studies have not been conducted with ZUTRIPRO Oral Solution. Other reported clinical experience with the individual active ingredients of ZUTRIPRO Oral Solution has not identified differences in responses between the elderly and patients younger than 65 years of age. In general, dose selection for an elderly patient should be made with caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. The pseudoephedrine contained in ZUTRIPRO Oral Solution is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Renal Impairment

ZUTRIPRO Oral Solution should be given with caution in patients with severe impairment of renal function. Pseudoephedrine is primarily excreted unchanged in the urine as unchanged drug with the remainder apparently being metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal impairment.

8.7 Hepatic Impairment

ZUTRIPRO Oral Solution should be given with caution in patients with severe impairment of hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ZUTRIPRO Oral Solution is a Schedule II controlled prescription containing hydrocodone bitartrate and should be prescribed and administered with caution.

9.2 Abuse

Hydrocodone can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of ZUTRIPRO Oral Solution, and it should be prescribed and administered with the same degree of caution appropriate to the use of other opioid drugs.

9.3 Dependence

Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, ZUTRIPRO Oral Solution should be prescribed and administered with caution.

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.

10 OVERDOSAGE

No human overdose data are available for ZUTRIPRO Oral Solution.

Hydrocodone:

Overdosage with hydrocodone 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, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Pseudoephedrine:

Overdosage with sympathomimetics such as pseudoephedrine may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscle weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusion and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsion, coma, and respiratory failure.

Chlorpheniramine:

Manifestations of chlorpheniramine overdose may vary from central nervous system depression to stimulation. Central toxic effects are characterized by agitation, anxiety, delirium, disorientation, hallucinations, hyperactivity, sedation, and seizures. Severe overdose may produce coma, medullary paralysis, and death. Peripheral toxicity includes hypertension, tachycardia, dysrhythmias, vasodilation, hyperpyrexia, mydriasis, urinary retention, and diminished gastrointestinal motility. Dry mouth, pharynx, bronchi, and nasal passages may be observed.

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

An adult ingested 400 mg chlorpheniramine with no reported serious adverse effects. Toxic psychosis, a possible class effect from overdose of sedating antihistamines, has been reported with accidental overdose of chlorpheniramine.

Treatment of overdose consists of discontinuation of ZUTRIPRO Oral Solution together with institution of appropriate therapy. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdose or unusual sensitivity to opioids including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

Hemodialysis is not routinely used to enhance the elimination of chlorpheniramine from the body. Urinary excretion of chlorpheniramine is increased when the pH of the urine is acidic; however, acid diuresis is NOT recommended to enhance elimination in overdose, as the risks of acidemia and acute tubular necrosis in patients with rhabdomyolysis far outweigh any potential benefit.

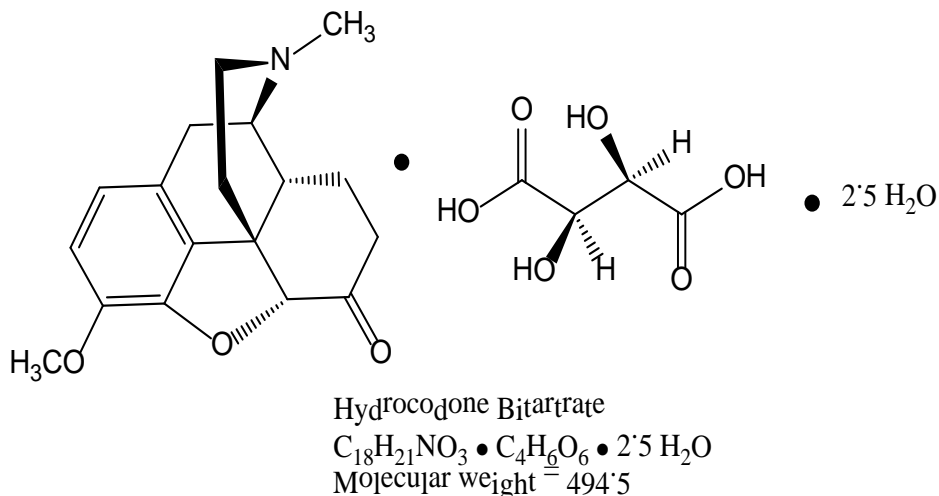
11 DESCRIPTION

ZUTRIPRO Oral Solution contains hydrocodone bitartrate (a semisynthetic centrally-acting opioid antitussive), chlorpheniramine maleate (an antihistamine), and pseudoephedrine hydrochloride (an indirect sympathomimetic amine).

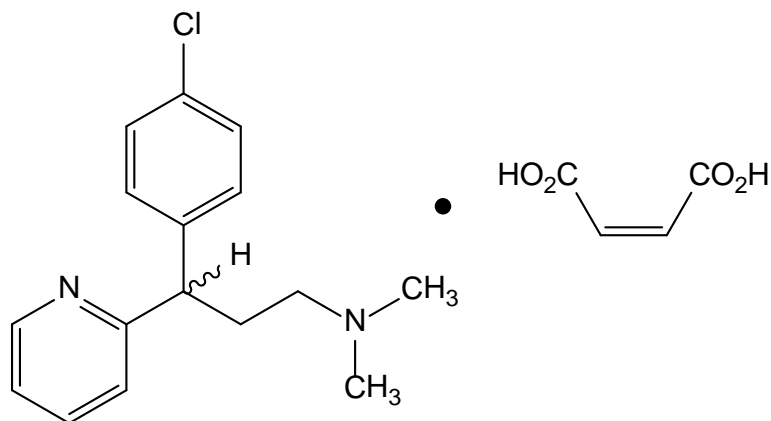
Each 5 mL dose of ZUTRIPRO Oral Solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg.

ZUTRIPRO Oral Solution also contains: citric acid anhydrous, glycerin, grape flavor, methylparaben, propylene glycol, propylparaben, purified water, sodium citrate, sodium saccharin, and sucrose.

Hydrocodone bitartrate is morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 α)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5); also known as 4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5); a fine white crystal or crystalline powder, which is derived from the opium alkaloid, thebaine; and may be represented by the following structural formula:

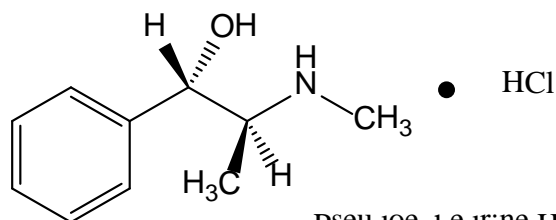


Chlorpheniramine maleate is 2-pyridinepropanamine, γ -(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1) and has the following chemical structure:



Chlorpheniramine Maleate
 $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$
Molecular weight = 390.86

Pseudoephedrine hydrochloride is benzenemethanol, α -[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)] hydrochloride and has the following chemical structure:



Pseudoephedrine Hydrochloride
 $C_{10}H_{15}NO \cdot HCl$
Molecular weight = 201.69

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and physiological dependence.

Chlorpheniramine is an antihistamine drug (H_1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to upper respiratory allergies or common cold. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

12.3 Pharmacokinetics

Systemic exposure (in terms of peak plasma concentrations and area under plasma concentration versus time curve) of hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride after single dose administration of 5 mL ZUTRIPRO Oral Solution are equivalent to respective reference solutions of 5 mL hydrocodone bitartrate (5 mg/5 mL), 5 mL chlorpheniramine maleate (4 mg/5 mL), and 5 mL pseudoephedrine hydrochloride (60 mg/5 mL).

Hydrocodone had mean (SD) peak plasma concentration of 10.6 (2.63) ng/mL at 1.4 (0.55) hours. The mean plasma half-life of hydrocodone is approximately 4.9 hours. Pseudoephedrine had a mean (SD) peak plasma concentration of 212 (46.2) ng/mL at 1.8 (0.56) hours. The mean plasma half-life of pseudoephedrine is approximately 5.6 hours. Chlorpheniramine had a mean (SD) plasma peak concentration of 7.20 (1.98) ng/mL at 3.5 (1.6) hours. The mean plasma half-life of chlorpheniramine is approximately 24 hours.

Specific Populations

Renal Impairment

Pseudoephedrine is primarily excreted unchanged in the urine as unchanged drug with the remainder apparently being metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with ZUTRIPRO Oral Solution; however, published information is available for the individual active ingredients or related active ingredients.

Hydrocodone:

Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 30 and 80 times, respectively, the MRHDD of hydrocodone on a mg/m² basis).

Chlorpheniramine:

In 2 year studies in F344/N rats and B6C3F1 mice, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses up to 30 and 50 mg/kg/day, respectively (approximately 15 times the MRHDD on a mg/m² basis).

Chlorpheniramine maleate was not mutagenic in the in vitro bacterial reverse mutation assay or the in vitro mouse lymphoma forward mutation assay. Chlorpheniramine maleate was clastogenic in the in vitro CHO cell chromosomal aberration assay.

Chlorpheniramine maleate had no effects on fertility in rats and rabbits at oral doses approximately 20 and 25 times the MRHDD on a mg/m² basis, respectively.

Pseudoephedrine:

Two-year feeding studies in rats and mice demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 0.3 and 0.5 times, respectively, the MRHDD of pseudoephedrine hydrochloride on a mg/m² basis).

14 CLINICAL STUDIES

Efficacy studies were not conducted with ZUTRIPRO Oral Solution. Efficacy of ZUTRIPRO Oral Solution is based on demonstration of bioequivalence to the individual reference products [*see Pharmacokinetics (12.3)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

ZUTRIPRO Oral Solution is supplied as a clear, colorless to light yellow, grape-flavored solution containing 5 mg hydrocodone bitartrate, 4 mg chlorpheniramine maleate, and 60 mg pseudoephedrine hydrochloride in each 5 mL. It is available in:

White HDPE bottles of one pint (480 mL): NDC 63717-876-16

Store solution at 20° to 25°C (68° to 77°F). [USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

17.1 Overdosage

Patients should be advised not to increase the dose or dosing frequency of ZUTRIPRO Oral Solution because serious adverse events such as respiratory depression may occur with overdosage [*see Warnings and Precautions (5.2); Overdosage (10)*].

17.2 Dosing

Patients should be advised to measure ZUTRIPRO Oral Solution with an accurate milliliter measuring device. Patients should be informed that a household teaspoon is not an accurate measuring device and could lead to overdosage, especially when half a teaspoon is measured. Patients should be advised to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose [*see Warnings and Precautions (5.10)*].

17.3 Interactions with Benzodiazepines and Other Central Nervous System Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if ZUTRIPRO Oral Solution is used with benzodiazepines or other CNS depressants, including alcohol. Because of this risk, patients should avoid concomitant use of ZUTRIPRO Oral Solution with benzodiazepines or other CNS depressants, including alcohol [*see Warnings and Precautions (5.1), Drug Interactions (7.1)*].

17.4 Activities Requiring Mental Alertness

Patients should be advised to avoid engaging in hazardous tasks that require mental alertness and motor coordination such as operating machinery or driving a motor vehicle as ZUTRIPRO Oral Solution may produce marked drowsiness [*see Warnings and Precautions (5.5)*].

17.5 Drug Dependence

Patients should be cautioned that ZUTRIPRO Oral Solution contains hydrocodone bitartrate and can produce drug dependence [*see Warnings and Precautions (5.3)*].

17.6 MAOIs

Patients should be informed that due to its pseudoephedrine component, they should not use ZUTRIPRO Oral Solution with a MAOI or within 14 days of stopping use of an MAOI [*see Warnings and Precautions (5.8)*].

Manufactured for: Hawthorn Pharmaceuticals, Inc., Morristown, NJ 07960
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Rev. 1/2017

MEDICATION GUIDE

ZUTRIPRO® (zoo-truh-proh)

(hydrocodone bitartrate, chlorpheniramine maleate and pseudoephedrine hydrochloride) Oral Solution, CII

What is the most important information I should know about ZUTRIPRO?

- Taking ZUTRIPRO with benzodiazepines, or other central nervous system depressants, including alcohol can cause severe drowsiness, breathing problems (respiratory depression), coma, and death.
- ZUTRIPRO can cause you to be drowsy. Avoid driving a car or operating machinery during treatment with ZUTRIPRO.
- Women who breastfeed should talk to their healthcare provider before taking ZUTRIPRO.
- Call your healthcare provider or get emergency medical help right away if anyone taking ZUTRIPRO has any of the symptoms below:
 - increased sleepiness
 - confusion
 - difficulty breathing
 - shallow breathing
 - limpness
 - your baby has difficulty breastfeeding
- Keep ZUTRIPRO in a safe place away from children. Accidental use by a child is a medical emergency and can cause death. If a child accidentally takes ZUTRIPRO, get emergency medical help right away.
- ZUTRIPRO can cause serious side effects, including death.
- Take ZUTRIPRO exactly as prescribed by your healthcare provider. If you take the wrong dose of ZUTRIPRO, you could overdose and die.
- ZUTRIPRO is not for children under 18 years of age.

What is ZUTRIPRO?

- ZUTRIPRO is a prescription medicine used in adults 18 years of age and older to treat:
 - a cough and nasal congestion that you can have with the common cold
 - symptoms including nasal congestion that you can have with upper respiratory allergies.ZUTRIPRO contains 3 medicines, hydrocodone and chlorpheniramine and pseudoephedrine. Hydrocodone is a narcotic cough suppressant. Chlorpheniramine is an antihistamine. Pseudoephedrine is a decongestant.
- **ZUTRIPRO is a federal controlled substance (C-II) because it contains hydrocodone that can be abused or lead to dependence.** Keep ZUTRIPRO in a safe place to prevent misuse and abuse. Selling or giving away ZUTRIPRO may harm others, and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- ZUTRIPRO is not for children under 18 years of age. It is not known if ZUTRIPRO is safe and effective in children.

Who should not take ZUTRIPRO?

- **Do not** take ZUTRIPRO if you are allergic to any of the ingredients in ZUTRIPRO. See the end of this Medication Guide for a complete list of ingredients. You may have an increased risk of having an allergic reaction to ZUTRIPRO if you are allergic to certain other opioid medicines.
- **Do not** take ZUTRIPRO if you take a medicine for depression called a Monoamine Oxidase Inhibitor (MAOI).
 - **Do not** take an MAOI within 14 days after you stop taking ZUTRIPRO.
 - **Do not** start ZUTRIPRO if you stopped taking an MAOI in the last 14 days.
- **Do not take** ZUTRIPRO if you have a type of glaucoma called “narrow angle glaucoma”.
- **Do not take** ZUTRIPRO if you have problems emptying your bladder (urinary retention).
- **Do not take** ZUTRIPRO if you have severe high blood pressure or certain heart problems (severe coronary artery disease).

Before you take ZUTRIPRO, tell your healthcare provider about all of your medical conditions, including if you:

- have a drug dependence
- have lung or breathing problems
- have had a head injury
- have pain in your stomach-area (abdomen)
- have a history of severe or persistent cough
- have prostate problems
- plan to have surgery
- drink alcohol
- have kidney or liver problems
- have diabetes
- have thyroid problems, such as hypothyroidism
- have Addison's disease

- have problems with your urinary tract (urethral stricture)
- are pregnant or plan to become pregnant. It is not known if ZUTRIPRO will harm your unborn baby. You and your healthcare provider should decide if you should take HYCODAN while you are pregnant.
- are breastfeeding or plan to breastfeed. Hydrocodone, chlorpheniramine, and pseudoephedrine pass into your breast milk. You and your healthcare provider should decide if you will take ZUTRIPRO or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking ZUTRIPRO with certain other medicines can cause side effects or affect how well ZUTRIPRO 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:

- take pain medicines such as narcotics
- take cold or allergy medicines that contain antihistamines or cough suppressants
- take medicines for mental illness (anti-psychotics, anti-anxiety)
- drink alcohol
- take medicines for depression, including monoamine oxidase inhibitors (MAOIs) and tricyclics
- take medicines for stomach or intestine problems

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

How should I take ZUTRIPRO?

- Take ZUTRIPRO exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much ZUTRIPRO to take and when to take it. Do not change your dose without talking to your healthcare provider.
- Take ZUTRIPRO by mouth only.
- ZUTRIPRO should be taken using an accurate milliliter measuring device.
- Ask your pharmacist to give you a measuring device to help you measure the correct amount of ZUTRIPRO. **Do not use a household teaspoon to measure your medicine. You may accidentally take too much.**
- If you take too much ZUTRIPRO, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking ZUTRIPRO?

- ZUTRIPRO can cause you to be drowsy. Avoid driving a car or operating machinery during treatment with ZUTRIPRO.
- Avoid drinking alcohol during treatment with ZUTRIPRO. Drinking alcohol can increase your chances of having serious side effects.

What are the possible side effects of ZUTRIPRO?

ZUTRIPRO may cause serious side effects, including:

- **See “What is the most important information I should know about ZUTRIPRO?”**
- **Breathing problems (respiratory depression) which can lead to death.** Call your healthcare provider or get emergency treatment right away if you are sleeping more than usual, have shallow or slow breathing, or confusion.
- **Physical dependence or abuse.** Take ZUTRIPRO exactly as your healthcare provider tells you to take it. Stopping ZUTRIPRO suddenly could cause withdrawal symptoms.
- **Increased intracranial pressure.**
- **Bowel problems including constipation or stomach pain.**
- **Heart and blood vessel (cardiovascular) and central nervous system (CNS) effects.** Cardiovascular and CNS effects can happen in some people during treatment with ZUTRIPRO, including trouble sleeping (insomnia), dizziness, weakness, tremors, abnormal heart beats (arrhythmias), seizures and feeling faint. Severe heart and blood vessel problems can also happen and cause you to have low blood pressure. Call your healthcare provider right away if you have any of these symptoms.

The most common side effects of ZUTRIPRO include:

- sleepiness
- confusion
- nausea and vomiting
- difficulty urinating
- trouble breathing
- mood changes, including: anxiety, fear, agitation, irritability, feeling high (euphoria) or feeling low (dysphoria)
- unable to control muscle movements in your face
- tiredness
- vision problems, including blurred vision
- headache
- feeling faint or lightheaded
- restlessness

These are not all the possible side effects of ZUTRIPRO.

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 ZUTRIPRO?

- Store ZUTRIPRO at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away medicine that is out of date or no longer needed.
- **Keep ZUTRIPRO Oral Solution and all medicines out of the reach of children.**

General information about the safe and effective use of ZUTRIPRO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZUTRIPRO for a condition for which it was not prescribed. Do not give ZUTRIPRO 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 ZUTRIPRO that is written for health professionals.

What are the ingredients in ZUTRIPRO?

Active ingredients: hydrocodone bitartrate, chlorpheniramine maleate and pseudoephedrine hydrochloride

Inactive ingredients: citric acid anhydrous, glycerin, grape flavor, methylparaben, propylene glycol, propylparaben, purified water, sodium citrate, sodium saccharin, and sucrose.

ZUTRIPRO is manufactured for Hawthorn Pharmaceuticals, Inc., Morristown, NJ 07960. ZUTRIPRO is a registered trademark of Hawthorn Pharmaceuticals, Inc.

For more information, go to www.ZUTRIPRO.com or call 1-800-793-2145.

CII Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride, and Chlorpheniramine Maleate Oral Solution

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride, and Chlorpheniramine Maleate Oral Solution safely and effectively. See full prescribing information for Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride, and Chlorpheniramine Maleate Oral Solution.

Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride, and Chlorpheniramine Maleate Oral Solution
Initial U.S. Approval: 2011

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.1)*]. Avoid use of opioid cough medications in patients taking benzodiazepines, CNS depressants, or alcohol.

RECENT MAJOR CHANGES

Boxed Warning	1/2017
Warnings and Precautions (5)	1/2017
Drug Interactions (7)	1/2017
Patient Counseling Information (17)	1/2017

INDICATIONS AND USAGE

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is a combination product containing an antitussive, an antihistamine, and a nasal decongestant indicated for:

- Relief of cough and nasal congestion associated with common cold (1.1)
- Relief of symptoms including nasal congestion associated with upper respiratory allergies (1.2)

Important Limitations of Use:

Not indicated for pediatric patients under 18 years of age

DOSAGE AND ADMINISTRATION

For Oral Use Only

- Adults 18 years of age and older: 5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours. (2)

DOSAGE FORMS AND STRENGTHS

Each 5 mL of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg. (3)

CONTRAINDICATIONS

- Patients with known hypersensitivity to hydrocodone bitartrate, pseudoephedrine hydrochloride, chlorpheniramine, or any of the inactive ingredients of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution. (4)
- Patients receiving monoamine oxidase inhibitor (MAOI) therapy or within 14 days of stopping such therapy. (4)
- Patients with narrow angle glaucoma, urinary retention, severe hypertension or severe coronary artery disease. (4)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

1 INDICATIONS AND USAGE

- 1.1 Common Cold
- 1.2 Upper Respiratory Allergies

2 DOSAGE AND ADMINISTRATION

- 2.1 Adults 18 Years of Age and Older

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

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Reference ID: 4041521

WARNINGS AND PRECAUTIONS

- Risks from Concomitant Use with Benzodiazepines or other CNS Depressants: Use with caution. (5.1)
- Drug Dependence: Prescribe with caution that is appropriate to the use of other opioids. (5.3)
- Head injury and increased intracranial pressure: Avoid in patients with head injury, intra-cranial lesions, or increased intracranial pressure. (5.3)
- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring complete mental alertness such as driving or operating machinery. (5.5)
- Avoid concurrent use of alcohol or other central nervous system depressants. (5.5)
- Acute abdominal conditions: Use with caution in patients with acute abdominal conditions. (5.6)
- Coexisting conditions: Use with caution in patients with diabetes, thyroid disease, Addison's disease, prostatic hypertrophy or urethral stricture, or asthma. (5.11)

ADVERSE REACTIONS

The most common adverse reactions of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution include: Sedation, somnolence, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, nervousness, or sleeplessness; blurred, double, or other visual disturbances; confusion, headache, euphoria, facial dyskinesia, feeling faint, lightheadedness, agitation, restlessness, insomnia, irritability, tremor. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Cypress Pharmaceutical, Inc. at tel: 1-800-793-2145 and www.cypressrx.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants: Avoid using with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution; May cause additive CNS depression. (7.1)
- MAOIs or tricyclic antidepressants: Do not use. May increase the effect of either the antidepressant or hydrocodone; may cause increase in blood pressure or hypertensive crisis may occur. (7.2)
- Anticholinergic drugs: Use with caution. Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, or constipation) may occur (7.3)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Use with caution in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use with caution in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 1/2017

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-

CII

FULL PRESCRIBING INFORMATION

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.1), Drug Interactions (7.1)*]. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.

1 INDICATIONS AND USAGE

1.1 Common Cold

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is indicated for relief of cough and nasal congestion associated with the common cold in adults 18 years of age and older.

1.2 Upper Respiratory Allergies

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is indicated for relief of symptoms including nasal congestion associated with upper respiratory allergies in adults 18 years of age and older.

Important Limitations of Use

Not indicated for pediatric patients under 18 years of age [see *Pediatric Use (8.4)*].

2 DOSAGE AND ADMINISTRATION

Administer hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution by the oral route only. Measure hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution with an accurate milliliter measuring device. Do not use a household teaspoon to measure the dose [see *Warnings and Precautions (5.10)*].

2.1 Adults 18 Years of Age and Older

5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

3 DOSAGE FORMS AND STRENGTHS

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is a clear, colorless to light yellow, grape-flavored liquid.

5 mL of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg [see *Description (11)*].

4 CONTRAINDICATIONS

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is contraindicated in:

- Patients with known hypersensitivity to hydrocodone bitartrate, pseudoephedrine hydrochloride, chlorpheniramine maleate, or any of the inactive ingredients of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution.
- Patients receiving MAOI therapy or within 14 days of stopping such therapy.
- Patients with narrow angle glaucoma, urinary retention, severe hypertension, or severe coronary artery disease.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Concomitant use of opioids, including hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate 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 Drug Interactions (7.1)*].

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 hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is used with benzodiazepines, alcohol, or other CNS depressants [*see Patient Counseling Information (17.3)*].

5.2 Respiratory Depression

Hydrocodone bitartrate, one of the active ingredients of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Overdose of hydrocodone bitartrate in adults has been associated with fatal respiratory depression, and the use of hydrocodone bitartrate in children less than 6 years of age has been associated with fatal respiratory depression. Exercise caution when administering hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution because of the potential for respiratory depression. If respiratory depression occurs, discontinue hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution and use naloxone hydrochloride when indicated to antagonize the effect and other supportive measures as necessary [*see Overdosage (10)*].

5.3 Drug Dependence

Hydrocodone can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution. Prescribe and administer hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral

solution with the same degree of caution appropriate to the use of other opioid drugs [*see Drug Abuse and Dependence (9.2, 9.3)*].

5.4 Head Injury and Increased Intracranial Pressure

The respiratory depression effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries. The use of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be avoided in these patients.

5.5 Activities Requiring Mental Alertness

Hydrocodone bitartrate and chlorpheniramine maleate, two of the active ingredients in hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate 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 hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution. Concurrent use of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution with alcohol or other central nervous system depressants should be avoided because additional impairment of central nervous system performance may occur.

5.6 Acute Abdominal Conditions

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be used with caution in patients with acute abdominal conditions since the administration of hydrocodone may obscure the diagnosis or clinical course of patients with acute abdominal conditions. The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus [*see Drug Interactions (7.3)*].

5.7 Co-administration with Anticholinergics

The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus. Exercise caution when using hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution in patients taking anticholinergic medications. [*see Drug Interactions (7.3)*].

5.8 Co-administration with MAOIs or Tricyclic Antidepressants

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should not be used in patients receiving MAOI therapy or within 14 days of stopping such therapy as an increase in blood pressure or hypertensive crisis, may occur. In addition, the use of MAOIs or tricyclic antidepressants with hydrocodone bitartrate, one of the active ingredients in hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, may increase the effect of either the antidepressant or hydrocodone [*see Contraindications (4) and Drug Interactions (7.2)*].

5.9 Cardiovascular and Central Nervous System Effects

The pseudoephedrine hydrochloride contained in hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution can produce cardiovascular and central nervous system effects in some patients such as insomnia, dizziness, weakness, tremor, or arrhythmias. In addition, central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension has been reported.

Therefore, hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be used with caution in patients with cardiovascular disorders, and should not be used in patients with severe hypertension or coronary artery disease.

5.10 Dosing

Patients should be advised to measure hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution with an accurate milliliter measuring device. Patients should be informed that a household teaspoon is not an accurate measuring device and could lead to overdose, which can result in serious adverse reactions [see *Overdosage (10)*]. Patients should be advised to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose.

5.11 Coexisting Conditions

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be used with caution in patients with diabetes, thyroid disease, Addison's disease, prostatic hypertrophy or urethral stricture, and asthma.

5.12 Renal Impairment

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be used with caution in patients with severe renal impairment [see *Use in Specific Populations (8.6)*; *Pharmacokinetics (12.3)*].

5.13 Hepatic Impairment

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be used with caution in patients with severe hepatic impairment [see *Use in Specific Populations (8.7)*].

6 ADVERSE REACTIONS

Use of hydrocodone bitartrate, a semisynthetic opioid, may result in the following:

- Respiratory depression [see *Warnings and Precautions (5.2)* and *Overdosage (10)*]
- Drug dependence [see *Warnings and Precautions (5.3)*]
- Increased intracranial pressure [see *Warnings and Precautions (5.4)* and *Overdosage (10)*]
- Decreased mental alertness with impaired mental and/or physical abilities [see *Warnings and Precautions (5.5)*]
- Paralytic ileus [see *Warnings and Precautions (5.6)*]

Use of pseudoephedrine, a sympathomimetic amine, may result in the following:

- Central nervous system effects such as insomnia, dizziness, weakness, tremor, or convulsions [see *Warnings and Precautions (5.9)*]
- Cardiovascular system effects such as arrhythmias, or increased blood pressure, cardiovascular collapse with accompanying hypotension [see *Warnings and Precautions (5.9)*]

Use of chlorpheniramine, an antihistamine, may result in:

- Decreased mental alertness with impaired mental and/or physical abilities [see *Warnings and Precautions (5.5)*]

The most common adverse reactions of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution include: Sedation, somnolence, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, nervousness, or sleeplessness; blurred, double, or other visual disturbances; confusion, headache, euphoria, facial dyskinesia, feeling faint, lightheadedness, agitation, restlessness, insomnia, irritability, tremor.

Other adverse reactions include:

Cardiovascular: Fast, or slow heartbeat, hypertension, hypotension, orthostatic hypotension, palpitations, shock-like state, syncope.

Respiratory: Dryness of the pharynx and respiratory passages, occasional tightness of the chest, laryngismus, wheezing, or troubled breathing.

Gastrointestinal System: Nausea and vomiting (more frequent in ambulatory than in recumbent patients), constipation, abdominal distension, abdominal pain, acute pancreatitis, dry mouth, dyspepsia, epigastric distress, and/or loss of appetite.

Genitourinary System: Ureteral spasm, spasm of vesicle sphincters, urinary retention, dysuria, urinary frequency, urinary hesitancy.

Dermatological System: Skin rash, pruritus, erythema, urticaria, excessive perspiration.

Endocrine System: Changes in glucose utilization, decreased lactation, early menses, glycosuria, gynecomastia, hypoglycemia, increased appetite, increased libido, pheochromocytoma stimulation.

Special Senses: labyrinthitis, tinnitus, vertigo, hypermetropia, lacrimation increased, mydriasis, photophobia.

7 DRUG INTERACTIONS

No specific interaction studies have been conducted with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution.

7.1 Benzodiazepines, Opioids, Antihistamines, Antipsychotics, Anti-anxiety Agents, or Other CNS Depressants (Including Alcohol)

The use of benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants concomitantly with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution may cause an additive CNS depressant effect, profound sedation, respiratory depression, coma, and death and should be avoided [*see Warnings and Precautions (5.1)*].

7.2 MAOIs and Tricyclic Antidepressants

Do not prescribe hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution if the patient is taking a prescription MAOI (i.e., certain drugs used for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping a MAOI drug. The use of MAOIs or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. An increase in blood pressure or hypertensive crisis may also occur when pseudoephedrine containing preparations are used with MAOIs [*see Warnings and Precautions (5.8)*].

7.3 Anticholinergic Drugs

Hydrocodone and chlorpheniramine should be administered cautiously to persons receiving other anticholinergic drugs in order to avoid paralytic ileus and excessive anticholinergic effects.

Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, or constipation) may occur when anticholinergic drugs are administered with chlorpheniramine [*see Warnings and Precautions (5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution in pregnant women. Reproductive toxicity studies have not been conducted with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution; however, studies are available with individual active ingredients or related active ingredients. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. A single retrospective study reported that chlorpheniramine was teratogenic in humans; however, the significance of these findings was not known. Developmental toxicity was also evident with chlorpheniramine in mice and rats. Because animal reproduction studies are not always predictive of human response, hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Hydrocodone:

Hydrocodone has been shown to be teratogenic in hamsters when given in a dose approximately 35 times the maximum recommended human daily dose (MRHDD) (on a mg/m² basis at a single subcutaneous dose of 102 mg/kg on gestation day 8). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In a study in which pregnant rats were dosed throughout organogenesis, a dose of codeine approximately 50 times the MRHDD of hydrocodone (on a mg/m² basis at an oral dose of 120 mg/kg/day of codeine) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, doses of codeine up to approximately 25 and 120 times, respectively, the MRHDD of hydrocodone (on a mg/m² basis at oral doses of 30 and 600 mg/kg/day, respectively), produced no adverse developmental effects.

Chlorpheniramine:

A retrospective study found a small, but statistically significant, association between maternal use of chlorpheniramine and inguinal hernia and eye or ear anomalies in children. Other retrospective studies have found that the frequency of congenital anomalies, in general, was not increased among offspring of women who took chlorpheniramine during pregnancy. The significance of these findings to the therapeutic use of chlorpheniramine in human pregnancy is not known.

In studies with chlorpheniramine in which pregnant rats and rabbits were dosed throughout organogenesis, oral doses up to approximately 20 and 25 times the MRHDD on a mg/m² basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, a dose approximately 5 times the MRHDD (on a mg/m² basis at an oral dose of 20 mg/kg/day) was embryo-lethal, and postnatal survival was decreased when dosing was continued after parturition. Embryo-lethality was also observed when male and

female rats were dosed with approximately 5 times the MRHDD (on a mg/m² basis at an oral dose of 10 mg/kg/day) prior to mating.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

8.2 Labor and Delivery

As with all opioids, administration of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

8.3 Nursing Mothers

Caution should be exercised when hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is administered to nursing mothers. Hydrocodone, chlorpheniramine and pseudoephedrine are excreted in human milk. The clinical significance is unknown; however, the anticholinergic action of chlorpheniramine may suppress lactation if taken prior to nursing. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution in pediatric patients under 18 years of age have not been established. The use of hydrocodone in children less than 6 years of age has been associated with fatal respiratory depression [*see Warnings and Precautions (5.2)*].

8.5 Geriatric Use

Clinical studies have not been conducted with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution. Other reported clinical experience with the individual active ingredients of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution has not identified differences in responses between the elderly and patients younger than 65 years of age. In general, dose selection for an elderly patient should be made with caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. The pseudoephedrine contained in hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Renal Impairment

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be given with caution in patients with severe impairment of renal function. Pseudoephedrine is primarily excreted

unchanged in the urine as unchanged drug with the remainder apparently being metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal impairment.

8.7 Hepatic Impairment

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be given with caution in patients with severe impairment of hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is a Schedule II controlled prescription containing hydrocodone bitartrate and should be prescribed and administered with caution.

9.2 Abuse

Hydrocodone can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, and it should be prescribed and administered with the same degree of caution appropriate to the use of other opioid drugs.

9.3 Dependence

Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be prescribed and administered with caution.

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.

10 OVERDOSAGE

No human overdose data are available for hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution.

Hydrocodone:

Overdosage with hydrocodone 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, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Pseudoephedrine:

Overdosage with sympathomimetics such as pseudoephedrine may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscle weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusion

and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsion, coma, and respiratory failure.

Chlorpheniramine:

Manifestations of chlorpheniramine overdose may vary from central nervous system depression to stimulation. Central toxic effects are characterized by agitation, anxiety, delirium, disorientation, hallucinations, hyperactivity, sedation, and seizures. Severe overdose may produce coma, medullary paralysis, and death. Peripheral toxicity includes hypertension, tachycardia, dysrhythmias, vasodilation, hyperpyrexia, mydriasis, urinary retention, and diminished gastrointestinal motility. Dry mouth, pharynx, bronchi, and nasal passages may be observed.

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

An adult ingested 400 mg chlorpheniramine with no reported serious adverse effects. Toxic psychosis, a possible class effect from overdose of sedating antihistamines, has been reported with accidental overdose of chlorpheniramine.

Treatment of overdose consists of discontinuation of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution together with institution of appropriate therapy. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdose or unusual sensitivity to opioids including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

Hemodialysis is not routinely used to enhance the elimination of chlorpheniramine from the body. Urinary excretion of chlorpheniramine is increased when the pH of the urine is acidic; however, acid diuresis is NOT recommended to enhance elimination in overdose, as the risks of acidemia and acute tubular necrosis in patients with rhabdomyolysis far outweigh any potential benefit.

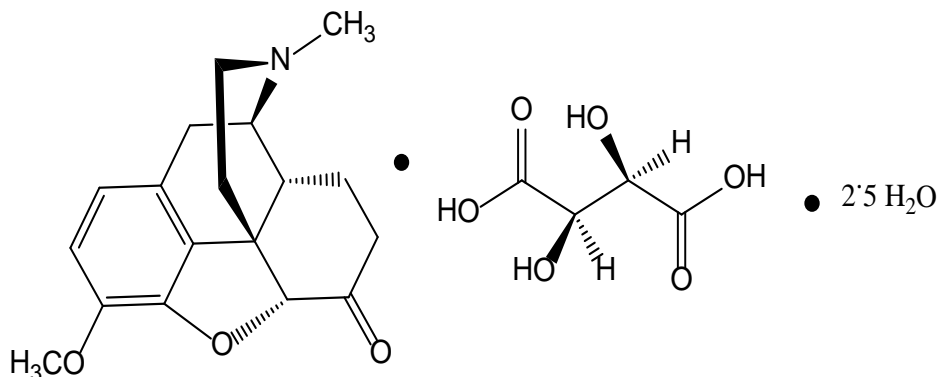
11 DESCRIPTION

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution contains hydrocodone bitartrate (a semisynthetic centrally-acting opioid antitussive), chlorpheniramine maleate (an antihistamine), and pseudoephedrine hydrochloride (an indirect sympathomimetic amine).

Each 5 mL dose of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg.

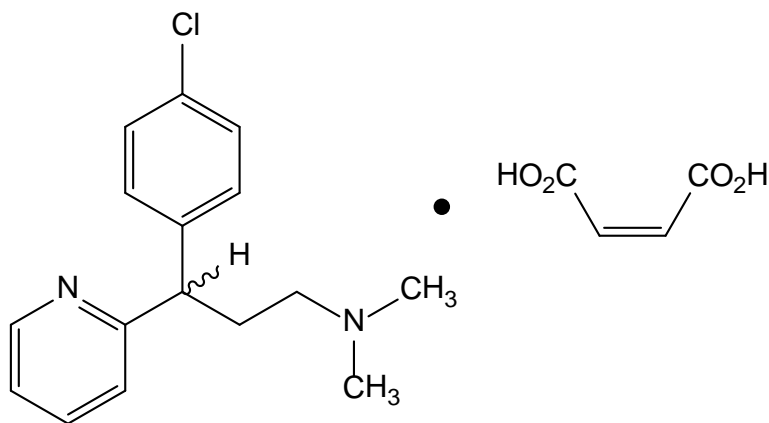
Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution also contains: citric acid anhydrous, glycerin, grape flavor, methylparaben, propylene glycol, propylparaben, purified water, sodium citrate, sodium saccharin, and sucrose.

Hydrocodone bitartrate is morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 α)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5); also known as 4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5); a fine white crystal or crystalline powder, which is derived from the opium alkaloid, thebaine; and may be represented by the following structural formula:



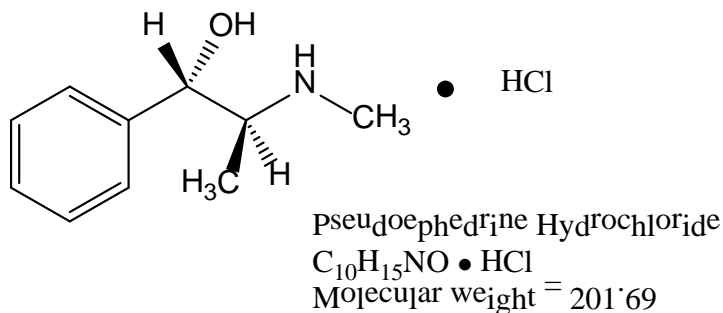
Hydrocodone Bitartrate
 $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2.5 H_2O$
Molecular weight = 494.5

Chlorpheniramine maleate is 2-pyridinepropanamine, γ -(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1) and has the following chemical structure:



Chlorpheniramine Maleate
 $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$
Molecular weight = 390.86

Pseudoephedrine hydrochloride is benzenemethanol, α -[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)] hydrochloride and has the following chemical structure:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and physiological dependence.

Chlorpheniramine is an antihistamine drug (H_1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to upper respiratory allergies or common cold. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

12.3 Pharmacokinetics

Systemic exposure (in terms of peak plasma concentrations and area under plasma concentration versus time curve) of hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride after single dose administration of 5 mL hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution are equivalent to respective reference solutions of 5 mL hydrocodone bitartrate (5 mg/5 mL), 5 mL chlorpheniramine maleate (4 mg/5 mL), and 5 mL pseudoephedrine hydrochloride (60 mg/5 mL).

Hydrocodone had mean (SD) peak plasma concentration of 10.6 (2.63) ng/mL at 1.4 (0.55) hours. The mean plasma half-life of hydrocodone is approximately 4.9 hours. Pseudoephedrine had a mean (SD) peak plasma concentration of 212 (46.2) ng/mL at 1.8 (0.56) hours. The mean plasma half-life of pseudoephedrine is approximately 5.6 hours. Chlorpheniramine had a mean (SD) plasma peak concentration of 7.20 (1.98) ng/mL at 3.5 (1.6) hours. The mean plasma half-life of chlorpheniramine is approximately 24 hours.

Specific Populations

Renal Impairment

Pseudoephedrine is primarily excreted unchanged in the urine as unchanged drug with the remainder apparently being metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution; however, published information is available for the individual active ingredients or related active ingredients.

Hydrocodone:

Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 30 and 80 times, respectively, the MRHDD of hydrocodone on a mg/m² basis).

Chlorpheniramine:

In 2 year studies in F344/N rats and B6C3F1 mice, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses up to 30 and 50 mg/kg/day, respectively (approximately 15 times the MRHDD on a mg/m² basis).

Chlorpheniramine maleate was not mutagenic in the in vitro bacterial reverse mutation assay or the in vitro mouse lymphoma forward mutation assay. Chlorpheniramine maleate was clastogenic in the in vitro CHO cell chromosomal aberration assay.

Chlorpheniramine maleate had no effects on fertility in rats and rabbits at oral doses approximately 20 and 25 times the MRHDD on a mg/m² basis, respectively.

Pseudoephedrine:

Two-year feeding studies in rats and mice demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 0.3 and 0.5 times, respectively, the MRHDD of pseudoephedrine hydrochloride on a mg/m² basis).

14 CLINICAL STUDIES

Efficacy studies were not conducted with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution. Efficacy of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is based on demonstration of bioequivalence to the individual reference products [see *Pharmacokinetics (12.3)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is supplied as a clear, colorless to light yellow, grape-flavored solution containing 5 mg hydrocodone bitartrate, 4 mg chlorpheniramine maleate, and 60 mg pseudoephedrine hydrochloride in each 5 mL. It is available in:

White HDPE bottles of one pint (480 mL): NDC 60258-876-16

Store solution at 20° to 25°C (68° to 77°F). [USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

17.1 Overdosage

Patients should be advised not to increase the dose or dosing frequency of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution because serious adverse events such as respiratory depression may occur with overdosage [see *Warnings and Precautions (5.2); Overdosage (10)*].

17.2 Dosing

Patients should be advised to measure hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution with an accurate milliliter measuring device. Patients should be informed that a household teaspoon is not an accurate measuring device and could lead to overdosage, especially when half a teaspoon is measured. Patients should be advised to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose [see *Warnings and Precautions (5.10)*].

17.3 Interactions with Benzodiazepines and Other Central Nervous System Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is used with benzodiazepines or other CNS depressants, including alcohol. Because of this risk, patients should avoid concomitant use of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution with benzodiazepines or other CNS depressants, including alcohol [see *Warnings and Precautions (5.1), Drug Interactions (7.1)*].

17.4 Activities Requiring Mental Alertness

Patients should be advised to avoid engaging in hazardous tasks that require mental alertness and motor coordination such as operating machinery or driving a motor vehicle as hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution may produce marked drowsiness [see *Warnings and Precautions (5.5)*].

17.5 Drug Dependence

Patients should be cautioned that hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution contains hydrocodone bitartrate and can produce drug dependence [see *Warnings and Precautions (5.3)*].

17.6 MAOIs

Patients should be informed that due to its pseudoephedrine component, they should not use hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution with a MAOI or within 14 days of stopping use of an MAOI [see *Warnings and Precautions (5.8)*].

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

Manufactured for: Cypress Pharmaceutical, Inc., Morristown, NJ 07960

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Rev. 1/2017

MEDICATION GUIDE

Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Chlorpheniramine Maleate Oral Solution, CII

What is the most important information I should know about hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?

- Taking hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution with benzodiazepines, or other central nervous system depressants, including alcohol can cause severe drowsiness, breathing problems (respiratory depression), coma, and death.
- Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution can cause you to be drowsy. Avoid driving a car or operating machinery during treatment with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution.
- Women who breastfeed should talk to their healthcare provider before taking hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution.
- Call your healthcare provider or get emergency medical help right away if anyone taking hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution has any of the symptoms below:
 - increased sleepiness
 - confusion
 - difficulty breathing
 - shallow breathing
 - limpness
 - your baby has difficulty breastfeeding
- Keep hydrocodone bitartrate, pseudoephedrine Hydrochloride, and chlorpheniramine maleate oral solution in a safe place away from children. Accidental use by a child is a medical emergency and can cause death. If a child accidentally takes hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, get emergency medical help right away.
- Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution can cause serious side effects, including death.
- Take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution exactly as prescribed by your healthcare provider. If you take the wrong dose of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, you could overdose and die.
- Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is not for children under 18 years of age.

What is hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?

- Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is a prescription medicine used in adults 18 years of age and older to treat:
 - a cough and nasal congestion that you can have with the common cold
 - symptoms including nasal congestion that you can have with upper respiratory allergies.Hydrocodone bitartrate, and pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution contains 3 medicines, hydrocodone and pseudoephedrine and chlorpheniramine. Hydrocodone is a narcotic cough suppressant. Pseudoephedrine is a decongestant. Chlorpheniramine is an antihistamine.
- **Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is a federal controlled substance (C-II) because it contains hydrocodone that can be abused or lead to dependence.** Keep hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution in a safe place to prevent misuse and abuse. Selling or giving away hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution may harm others, and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is not for children under 18 years of age. It is not known if hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution is safe and effective in children.

Who should not take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?

- **Do not** take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution if you are allergic to any of the ingredients in hydrocodone bitartrate, pseudoephedrine hydrochloride, and

chlorpheniramine maleate oral solution. See the end of this Medication Guide for a complete list of ingredients. You may have an increased risk of having an allergic reaction to hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution if you are allergic to certain other opioid medicines.

- **Do not** take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution if you take a medicine for depression called a Monoamine Oxidase Inhibitor (MAOI).
 - **Do not** take an MAOI within 14 days after you stop taking hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution.
 - **Do not** start hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution if you stopped taking an MAOI in the last 14 days.
- **Do not take** hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution if you have a type of glaucoma called “narrow angle glaucoma”.
- **Do not take** hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution if you have problems emptying your bladder (urinary retention).
- **Do not take** hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution if you have severe high blood pressure or certain heart problems (severe coronary artery disease).

Before you take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, tell your healthcare provider about all of your medical conditions, including if you:

- have a drug dependence
- have lung or breathing problems
- have had a head injury
- have pain in your stomach-area (abdomen)
- have a history of severe or persistent cough
- have prostate problems
- have problems with your urinary tract (urethral stricture)
- are pregnant or plan to become pregnant. It is not known if hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution will harm your unborn baby. You and your healthcare provider should decide if you should take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution while you are pregnant.
- are breastfeeding or plan to breastfeed. Hydrocodone bitartrate, pseudoephedrine hydrochloride, chlorpheniramine, and chlorpheniramine maleate oral solution pass into your breast milk. You and your healthcare provider should decide if you will take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution or breastfeed. You should not do both.
- plan to have surgery
- drink alcohol
- have kidney or liver problems
- have diabetes
- have thyroid problems, such as hypothyroidism
- have Addison’s disease
- have a dry mouth

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution with certain other medicines can cause side effects or affect how well hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate 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:

- take pain medicines such as narcotics
- take cold or allergy medicines that contain antihistamines or cough suppressants
- take medicines for mental illness (anti-psychotics, anti-anxiety)
- drink alcohol
- take medicines for depression, including monoamine oxidase inhibitors (MAOIs) and tricyclics
- take medicines for stomach or intestine problems.

How should I take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?

- Take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution to take and when to take it. Do not change your dose without talking to your healthcare provider.
- Take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution only by mouth.
- Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution should be taken using an accurate milliliter measuring device.
- Ask your pharmacist to give you a measuring device to help you measure the correct amount of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution. **Do not use a household teaspoon to measure your medicine. You may accidentally take too much.**
- If you take too much hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?

- Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution can cause you to be drowsy. Avoid driving a car or operating machinery during treatment with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution.
- Avoid drinking alcohol during treatment with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution. Drinking alcohol can increase your chances of having serious side effects.

What are the possible side effects of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?

Hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution may cause serious side effects, including:

- See “What is the most important information I should know about hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?”
- **Breathing problems (respiratory depression) which can lead to death.** Call your healthcare provider or get emergency treatment right away if you are sleeping more than usual, have shallow or slow breathing, or confusion.
- **Physical dependence or abuse.** Take hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution exactly as your healthcare provider tells you to take it. Stopping hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution suddenly could cause withdrawal symptoms.
- **Bowel problems including constipation or stomach pain.**
- **Heart and blood vessel (cardiovascular) and central nervous system (CNS) effects.** Cardiovascular and CNS effects can happen in some people during treatment with hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution, including trouble sleeping (insomnia), dizziness, weakness, tremors, abnormal heart beats (arrhythmias), seizures and feeling faint. Severe heart and blood vessel problems can also happen and cause you to have low blood pressure. Call your healthcare provider right away if you have any of these symptoms.

The most common side effects of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution include:

- | | |
|---|---|
| • sleepiness | • tiredness |
| • confusion | • vision problems, including blurred vision |
| • nausea and vomiting | • headache |
| • difficulty urinating | • feeling faint or lightheaded |
| • trouble breathing | • restlessness |
| • mood changes, including: anxiety, fear, agitation, irritability, feeling high (euphoria) or feeling low (dysphoria) | |

- unable to control muscle movements in your face

These are not all the possible side effects of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate 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 hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?

- Store hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away medicine that is out of date or no longer needed.
- **Keep hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution and all medicines out of the reach of children.**

General information about the safe and effective use of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution for a condition for which it was not prescribed. Do not give hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate 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 hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution that is written for health professionals.

What are the ingredients in hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate oral solution?

Active ingredients: hydrocodone bitartrate, pseudoephedrine hydrochloride and chlorpheniramine maleate

Inactive ingredients: citric acid anhydrous, glycerin, grape flavor, methylparaben, propylene glycol, propylparaben, purified water, sodium citrate, sodium saccharin, and sucrose.

Manufactured for: Cypress Pharmaceutical, Inc., Morristown, NJ 07960.

For more information, call 1-800-793-2145.