

**CIII 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**

-----**RECENT MAJOR CHANGES**-----

-----**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**-----

- Dose-related respiratory depression: Use with caution. (5.1)
- Drug Dependence: Prescribe with caution that is appropriate to the use of other opioids. (5.2)
- 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. (5.4)
- Avoid concurrent use of alcohol or other central nervous system depressants. (5.4)
- Acute abdominal conditions: Use with caution in patients with acute abdominal conditions. (5.5)
- Coexisting conditions: Use with caution in patients with diabetes, thyroid disease, Addison's disease, prostatic hypertrophy or urethral stricture, or asthma. (5.10)

-----**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: 1-800-856-4393 and www.hawthornrx.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

-----**DRUG INTERACTIONS**-----

- 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**

**Revised: [05/06/2011]**

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\*Sections or subsections omitted from the full prescribing information are not listed.

## **CIII**

### **FULL PRESCRIBING INFORMATION**

#### **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 (5.9)*].

##### **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 Respiratory Depression**

Hydrocodone bitartrate, one of the active ingredients in 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)*].

### **5.2 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)*].

### **5.3 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.

### **5.4 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.

### **5.5 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)*].

## 5.6 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)*].

## 5.7 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)*].

## 5.8 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.

## 5.9 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.

## 5.10 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.

## 5.11 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)*].

## 5.12 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 (5.1) and Overdosage (10)*]
- Drug dependence [*see Warnings and Precautions (5.2)*]
- Increased intracranial pressure [*see Warnings and Precautions (5.3) and Overdosage (10)*]
- Decreased mental alertness with impaired mental and/or physical abilities [*see Warnings and Precautions (5.4)*]
- Paralytic ileus [*see Warnings and Precautions (5.5)*]

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 (5.8)*]
- Cardiovascular system effects such as arrhythmias, or increased blood pressure, cardiovascular collapse with accompanying hypotension [*see Warnings and Precautions (5.8)*]

Use of chlorpheniramine, an antihistamine, may result in:

- Decreased mental alertness with impaired mental and/or physical abilities [*see Warnings and Precautions (5.4)*]

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

The use of opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants concomitantly with ZUTRIPRO Oral Solution may cause an additive CNS depressant effect and should be avoided.

### **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* (5.7)].

### **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* (5.6)].

## 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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, a dose approximately 5 times the MRHDD (on a  $\text{mg}/\text{m}^2$  basis at an oral dose of 20 mg/kg/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  $\text{mg}/\text{m}^2$  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 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 (5.1)*].

## **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 III 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 overdosage 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 overdosage, 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 overdosage 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 overdosage 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 overdosage 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 overdosage 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.

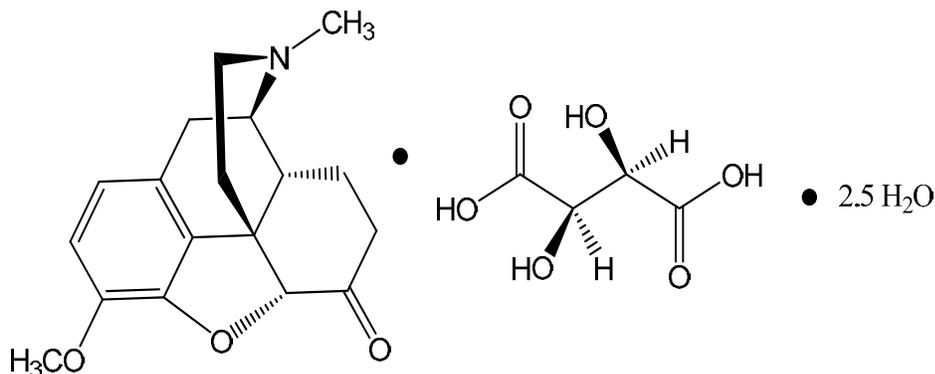
## **11 DESCRIPTION**

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.

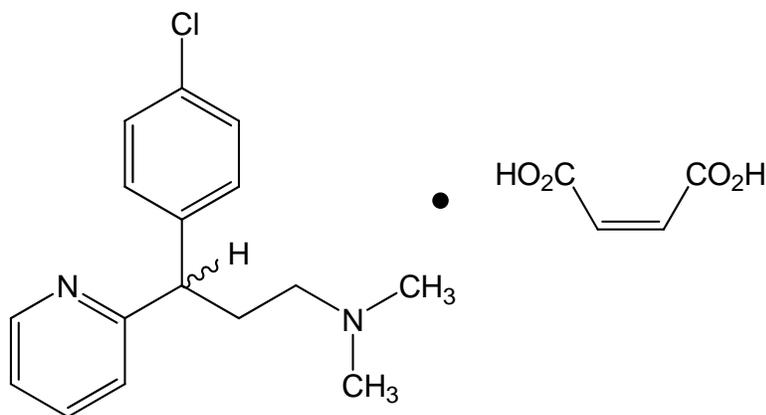
ZUTRIPRO Oral Solution also contains: citric acid anhydrous, glycerin, grape flavor, methylparaben, propylene glycol, propylparaben, purified water, sodium citrate, sodium saccharin, and sucrose.

Hydrocodone bitartrate is morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 $\alpha$ )-, [R-(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5); also known as 4,5 $\alpha$ -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:



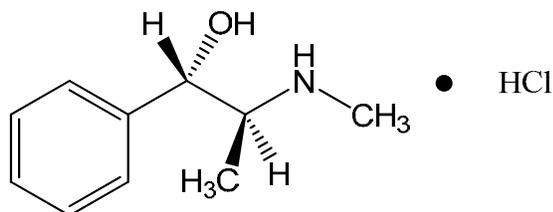
Hydrocodone Bitartrate  
 $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2.5 H_2O$   
Molecular weight = 494.5

Chlorpheniramine maleate is 2-pyridinepropanamine,  $\gamma$ -(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,  $\alpha$ -[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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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 (5.1); 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 (5.9)*].

### 17.3 Concomitant Use of Alcohol and Other Central Nervous System Depressants

Patients should be advised to avoid the use of alcohol and other central nervous system depressants while taking ZUTRIPRO Oral Solution because additional reduction in mental alertness may occur [see *Warnings and Precautions (5.4)*].

### 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 (5.4)*].

### 17.5 Drug Dependence

Patients should be cautioned that ZUTRIPRO Oral Solution contains hydrocodone bitartrate and can produce drug dependence [see *Warnings and Precautions (5.2)*].

## 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 (5.7)*].

Manufactured for: Hawthorn Pharmaceuticals, Inc., Madison, MS 39110

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