

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207768Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TUZISTRA™ XR safely and effectively. See full prescribing information for TUZISTRA XR.

TUZISTRA XR (codeine polistirex and chlorpheniramine polistirex) extended-release oral suspension, CIII
Initial U.S. Approval: 1985

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE

See full prescribing information for complete boxed warning.

Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism. (5.1)

INDICATIONS AND USAGE

TUZISTRA XR is a combination of codeine, an opiate agonist antitussive, and chlorpheniramine, a histamine-1 (H₁) receptor antagonist indicated for relief of cough and symptoms associated with upper respiratory allergies or a common cold. (1.1)

Limitation of Use:

Not indicated for pediatric patients under 18 years of age. (1.1)

DOSAGE AND ADMINISTRATION

- Adults 18 years of age and older: 10 mL every 12 hours. Not to exceed 2 doses (20 mL) in 24 hours. (2.1)
- For Oral Use Only, with or without food. (2.2)

DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension contains: an antitussive – codeine polistirex, which contains 14.7 mg of codeine (equivalent to 20 mg codeine phosphate), and an antihistamine – chlorpheniramine polistirex, which contains 2.8 mg of chlorpheniramine (equivalent to 4 mg chlorpheniramine maleate) per 5 mL. (3)

CONTRAINDICATIONS

- Postoperative pain management of children undergoing tonsillectomy and/or adenoidectomy. (4)
- Patients with known hypersensitivity to codeine, chlorpheniramine, or any of the product components of TUZISTRA XR. (4)

WARNINGS AND PRECAUTIONS

- Risk of death in ultra-rapid metabolizers: Conversion of codeine into its active metabolite, morphine, may occur more rapidly and completely resulting in higher than expected morphine levels and respiratory depression or death. (5.1)
- Dose-related respiratory depression: Use with caution. (5.2)
- 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 heavy machinery. 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. (5.7)
- Special risk patients: Caution in elderly patients and those with asthma, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. (5.9)

ADVERSE REACTIONS

Common adverse reactions of TUZISTRA XR include: nausea and vomiting, constipation, abdominal distension, abdominal pain, blurred vision, diplopia, visual disturbances, confusion, dizziness, depression, drowsiness, sedation, headache, euphoria, facial dyskinesia, feeling faint, light-headedness, general feeling of discomfort or illness, excitability, nervousness, agitation, restlessness, somnolence, insomnia, dyskinesia, irritability, tremor. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Vernalis Therapeutics, Inc. 1-855-705-9546 and www.vernalistherapeutics.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: May cause additive CNS depression. (7.1)
- MAOIs or tricyclic antidepressants: May increase the effect of either the antidepressant or codeine. (7.2)
- Anticholinergic drugs: Use with caution. Additive adverse effects resulting from cholinergic blockage (e.g., xerostomia, blurred vision, or constipation) may occur. (7.3)
- Inhibitors or inducers of metabolic enzymes: Concomitant use of cytochrome P450 2D6 and 3A4 enzyme inhibitors or inducers may result in an altered response to codeine, monitor antitussive activity. Chlorpheniramine may inhibit the hepatic metabolism of phenytoin, monitor phenytoin toxicity. (7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Labor: Use of codeine during labor can produce respiratory depression in the neonate. (8.2)
- Nursing mothers: The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby. (8.3)
- Pediatric patients: Safety and effectiveness of this drug product has not been established for patients under 18 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

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Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism [see [Warnings and Precautions \(5.1\)](#)].

1 INDICATIONS AND USAGE

1.1 Cough and Upper Respiratory Allergy Symptoms

TUZISTRA XR is indicated for the relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults 18 years of age and older.

Important Limitations of Use

Not indicated for pediatric patients under 18 years of age [see [Use in Specific Populations \(8.4\)](#)].

2 DOSAGE AND ADMINISTRATION

2.1 Adults 18 Years of Age and Older

TUZISTRA XR should be orally administered in a dose of 10 mL every 12 hours, not to exceed 2 doses (20 mL) in 24 hours.

2.2 Administration Information

Administer TUZISTRA XR by the oral route only, with or without food. Shake well before use. Measure with an accurate milliliter measuring device. Do not use a household teaspoon to measure the dose [see [Warnings and Precautions \(5.8\)](#)].

3 DOSAGE FORMS AND STRENGTHS

TUZISTRA XR is a pink to reddish pink, cherry-flavored liquid oral suspension.

Extended-release oral suspension contains: codeine polistirex, which contains 14.7 mg of codeine (equivalent to 20 mg codeine phosphate), and chlorpheniramine polistirex, which contains 2.8 mg of chlorpheniramine (equivalent to 4 mg chlorpheniramine maleate) per 5 mL [see [Description \(11\)](#) and [How Supplied/Storage and Handling \(16\)](#)].

4 CONTRAINDICATIONS

TUZISTRA XR is contraindicated in:

- Postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy [see [Warnings and Precautions \(5.1\)](#)].
- Patients with known hypersensitivity to codeine, chlorpheniramine or any of the inactive ingredients of TUZISTRA XR. Persons known to be hypersensitive to certain other opioids may exhibit cross-sensitivity to codeine.

5 WARNINGS AND PRECAUTIONS

5.1 Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 [CYP2D6] or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine [see [Use in Specific Populations \(8.3\)](#)].

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see [Overdosage \(10\)](#)].

Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for postoperative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see [Contraindications \(4\)](#)].

When prescribing codeine-containing drugs, healthcare professionals should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose [see [Use in Specific Populations \(8\)](#), [Overdosage \(10\)](#)].

5.2 Respiratory Depression

Codeine, one of the active ingredients in TUZISTRA XR, produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Codeine affects the center that controls respiratory rhythm and may produce irregular and periodic breathing. Caution should be exercised when TUZISTRA XR is used postoperatively, in patients with pulmonary disease or shortness of breath, or whenever ventilator function is depressed.

Overdose of codeine in adults has been associated with fatal respiratory depression, and the use of codeine in children has been associated with fatal respiratory depression. Exercise caution when administering TUZISTRA XR because of the potential for respiratory depression. If respiratory depression occurs, discontinue TUZISTRA XR and use naloxone hydrochloride when indicated to antagonize the effect and other supportive measures as necessary [see [Overdosage \(10\)](#)].

5.3 Drug Dependence

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of TUZISTRA XR. Prescribe and administer TUZISTRA XR 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 that may obscure the clinical course of patients with head injuries. The use of TUZISTRA XR should be avoided in these patients.

5.5 Activities Requiring Mental Alertness

Codeine and chlorpheniramine, the active ingredients in TUZISTRA XR, 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 TUZISTRA XR. Concurrent use of TUZISTRA XR with alcohol or other central nervous system depressants should be avoided because additional impairment of central nervous system performance may occur.

5.6 Obstructive Bowel Disease

Chronic use of opioids, including codeine, may result in constipation or obstructive bowel disease especially in patients with underlying intestinal motility disorders. Use with caution in patients with underlying intestinal motility disorders.

5.7 Acute Abdominal Conditions

TUZISTRA XR should be used with caution in patients with acute abdominal conditions since the administration of codeine may obscure the diagnosis or clinical course of patients with acute abdominal conditions. The concurrent use of other anticholinergics with codeine may produce paralytic ileus [see [Drug Interactions \(7.3\)](#)]

5.8 Dosing

Patients should be advised to measure TUZISTRA XR 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.

5.9 Special Risk Patients

As with other opioids, TUZISTRA XR should be used with caution in elderly or debilitated patients and those with asthma, persistent or chronic cough, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed, and the possibility of respiratory depression should be kept in mind.

6 ADVERSE REACTIONS

Use of codeine, 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 \(5.7\)](#)]

Use of chlorpheniramine, an antihistamine, may result in:

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

Adverse reactions listed below have been reported in the literature for codeine and chlorpheniramine and may be expected to occur with TUZISTRA XR. Also included are events that occurred during clinical pharmacokinetic studies (in a total of 66 healthy adult volunteers with either single or multiple dose exposure) with TUZISTRA XR and judged by the investigator to be related to study treatment. Because these reactions may be reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergic: Allergic laryngospasm, nasal stuffiness, bronchospastic allergic reaction, hives, itching, swelling of face.

Body as a whole: Asthenia, feeling of relaxation, redness or flushing of the face, unusual tiredness, weakness.

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

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

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

Gastrointestinal System: Nausea and vomiting, constipation, abdominal distension, abdominal pain, acute pancreatitis, dry mouth, dyspepsia, epigastric distress, loss of appetite, diarrhea, gastro-esophageal reflux, gastrointestinal hypomotility.

Genitourinary System: Ureteral spasm, urinary retention, dysuria, urinary frequency, urinary hesitancy, irritative bladder symptom.

Nervous System: Blurred vision, diplopia, visual disturbances, confusion, dizziness, depression, drowsiness, sedation, headache, euphoria, facial dyskinesia, false sense of well-being, feeling faint, lightheadedness, general feeling of discomfort or illness, excitability, nervousness, agitation, restlessness, somnolence, insomnia, dyskinesia, irritability, tremor.

Respiratory: Dryness of the pharynx and respiratory passages, laryngismus, atelectasis, wheezing, troubled breathing, respiratory depression, hiccups.

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

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with TUZISTRA XR.

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 (including alcohol) concomitantly with TUZISTRA XR may cause an additive CNS depressant effect and should be avoided.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Do not prescribe TUZISTRA XR if the patient is taking a monoamine oxidase inhibitor (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 codeine preparations may increase the effect of either the antidepressant or codeine.

7.3 Anticholinergic Drugs

Codeine 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.

7.4 Inhibitors or Inducers of Metabolic Enzymes

Codeine is metabolized by the CYP2D6 and CYP3A4 isoenzymes [see [Clinical Pharmacology \(12.3\)](#)]. The concurrent use of drugs that preferentially induce codeine N-demethylation (via CYP3A4) may increase the plasma concentrations of codeine's inactive metabolite norcodeine. Drugs that inhibit codeine O-demethylation (via CYP2D6) may decrease the plasma concentration of codeine's active metabolites, morphine and morphine-6-glucuronide. The contribution of these active metabolites to the overall antitussive effect of codeine is not known but should be considered.

Adverse event reports in the literature suggest a possible drug interaction involving increased serum phenytoin levels and phenytoin toxicity when chlorpheniramine and phenytoin are co-administered. The exact mechanism for this interaction is not known, however it is believed that chlorpheniramine may inhibit the hepatic metabolism of phenytoin. Patients should be monitored for evidence of phenytoin toxicity such as ataxia, hyperreflexia, nystagmus and tremor when these two drugs are co-administered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Teratogenic Effects

There are no adequate and well-controlled studies of TUZISTRA XR in pregnant women.

Reproductive toxicity studies have not been conducted with TUZISTRA XR; however, studies are available with individual active ingredients or related active ingredients. Because animal reproduction studies are not always predictive of human response, TUZISTRA XR should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Codeine:

Codeine has embryo-lethal and fetotoxic effects in rats. In a study in which pregnant rats were dosed throughout organogenesis, a dose approximately 20 times the maximum recommended human daily dose (MRHDD; on a mg/m² basis at an oral maternal dose of 120 mg/kg/day) 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, codeine at doses approximately 9 and 45 times the MRHDD (on a mg/m² basis at 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 25 and 30 times the MRHDD on a mg/m² basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, a dose approximately 9 times the MRHDD (on a mg/m² basis at an oral maternal 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 9 times the MRHDD (on a mg/m² basis at an oral parental dose of 10 mg/kg/day) prior to mating.

Nonteratogenic Effects

Codeine:

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 TUZISTRA XR 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 TUZISTRA XR is administered to nursing mothers. Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk.

and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breast-feeding [see [Warnings and Precautions \(5.1\)](#)].

Chlorpheniramine is excreted in human milk. The clinical significance is unknown; however, the anticholinergic action of chlorpheniramine may suppress lactation if taken prior to nursing.

8.4 Pediatric Use

Safety and effectiveness of TUZISTRA XR in pediatric patients under 18 years of age have not been established. The use of codeine in children has been associated with fatal respiratory depression [see [Warnings and Precautions \(5.1, 5.2\)](#)].

8.5 Geriatric Use

Clinical efficacy and safety studies have not been conducted with TUZISTRA XR. Other reported clinical experience with the individual active ingredients of TUZISTRA XR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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.

8.6 Renal Impairment

Pharmacokinetics of TUZISTRA XR has not been characterized in renal impairment subjects. Both codeine and chlorpheniramine are cleared substantially by the kidney. As such, impaired renal function could potentially lead to the risk of decreased clearance and thereby increased retention or systemic levels of both these drugs. TUZISTRA XR should be used with caution in patients with severe renal impairment.

8.7 Hepatic Impairment

Pharmacokinetics of TUZISTRA XR has not been characterized in hepatic impairment subjects. Both codeine and chlorpheniramine are extensively metabolized by the liver before elimination from the body. As such, impaired hepatic function could potentially lead to the risk of decreased metabolism and thereby increased systemic levels of both these drugs. TUZISTRA XR should be used with caution in patients with severe hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TUZISTRA XR is a Schedule III controlled prescription product containing codeine and should be prescribed and administered with caution.

9.2 Abuse

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

9.3 Dependence

Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, TUZISTRA XR 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 TUZISTRA XR.

Codeine:

Overdosage with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur.

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

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 TUZISTRA XR together with institution of appropriate therapy.

Give primary attention to re-establishment 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 that may result from overdosage or unusual sensitivity to opioids including codeine. 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 or circulatory 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 codeine or 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 benefits.

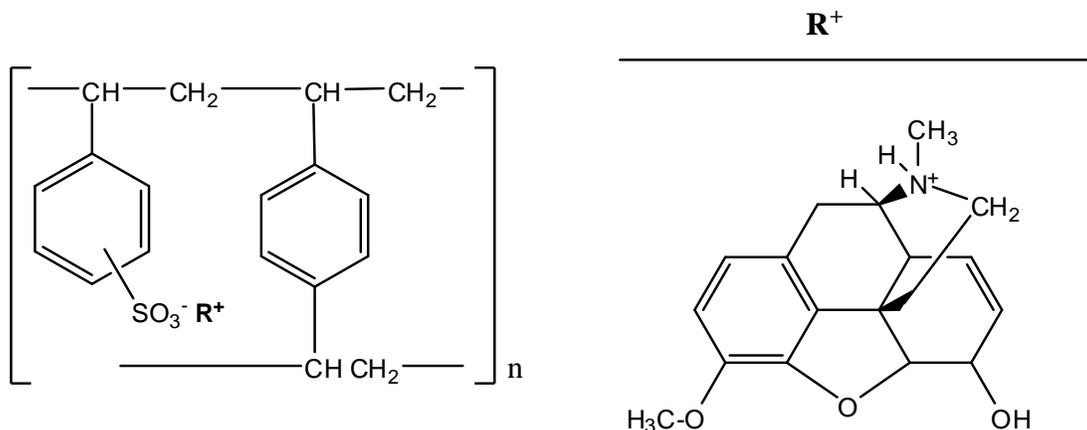
11 DESCRIPTION

TUZISTRA XR (codeine polistirex and chlorpheniramine polistirex) extended-release oral suspension is a pink to reddish pink, cherry-flavored liquid suspension that contains an opiate agonist antitussive codeine and a histamine-1 (H₁) receptor antagonist (antihistamine) chlorpheniramine. Each 5 mL of TUZISTRA

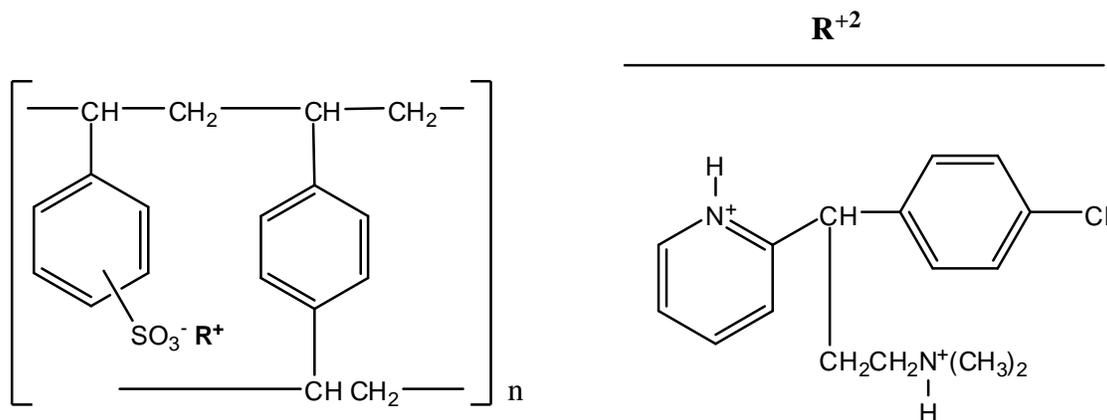
XR contains 14.7 mg of codeine (equivalent to 20 mg of codeine phosphate) and 2.8 mg of chlorpheniramine (equivalent to 4 mg of chlorpheniramine maleate) bound to sulfonated styrene-divinylbenzene copolymer (polistirex).

TUZISTRA XR contains the following inactive ingredients: cherry flavor, citric acid, D&C Red No. 30, ethyl maltol, glycerin, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propyl gallate, propylparaben, purified water, sodium citrate, sodium polystyrene sulfonate, starch, sucrose, triacetin, xanthan gum.

Codeine is (5 α ,6 α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol, has the following molecular formula, C₁₈H₂₁NO₃, and a molecular weight of 299.36. Codeine polistirex is a complex of codeine with sulfonated styrene-divinylbenzene copolymer, having the following structural formula:



Chlorpheniramine is γ -(4-chlorophenyl)-*N,N*-dimethyl-2-pyridinepropanamine, has the following molecular formula, C₁₆H₁₉ClN₂, and a molecular weight of 274.80. Chlorpheniramine polistirex is a complex of chlorpheniramine with sulfonated styrene-divinylbenzene copolymer, having the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Chlorpheniramine is a propylamine derivative antihistamine drug (H₁ receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

12.3 Pharmacokinetics

Absorption

Pharmacokinetic (PK) parameters (Mean ± SD) for TUZISTRA XR (codeine polistirex and chlorpheniramine polistirex) extended-release oral suspension in fasting, healthy volunteers are shown in the table below.

PK Parameter	Single-dose		Multiple-dose (BID for 7 days)	
	Codeine Mean (± SD)	Chlorpheniramine Mean (± SD)	Codeine Mean (± SD)	Chlorpheniramine Mean (± SD)
T _{max} (h) (Range)	2.19 (1-4.05)	6.52 (5-9)	1.86 (0.5-3)	5.77 (2.5-9.5)
C _{max} (ng/mL)	51.4 (± 13.8)	7.84 (± 1.84)	64.6 (± 21.9)	38.7 (± 15.2)
AUC _{inf} (ng·h/mL) for single-dose OR AUC ₀₋₁₂ (ng·h/mL) for multiple-dose	348.5 (± 94)	304.3 (± 104)	384.8 (± 128)	392.4 (± 147)
Half-life (h)	5 (± 1.07)	21.45 (± 5.87)	Not determined	Not determined

Food Effect:

The presence of a high-fat, high calorie meal did not significantly impact TUZISTRA XR pharmacokinetics.

Distribution

Codeine has been reported to have an apparent volume of distribution of approximately 3 to 6 L/kg, indicating extensive distribution of the drug into tissues. About 7 to 25% of codeine, reportedly, is bound to plasma proteins. Codeine passes the blood brain barrier and the placental barrier. Small amounts of codeine and its metabolite, morphine, are transferred to human breast milk.

Chlorpheniramine is widely distributed throughout the tissues of the body, including the central nervous system. It reportedly has an apparent steady-state volume of distribution of approximately 3.2 L/kg in adults and children and is about 70% bound to plasma proteins. Chlorpheniramine and its metabolites likely cross the placental barrier and are excreted into human breast milk.

Metabolism

About 70-80% of the administered dose of codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide (C6G) and via O-demethylation to morphine (about 5-10%) and N-demethylation to norcodeine (about 10%) respectively. UDP-glucuronosyltransferase (UGT) 2B7 and 2B4 are the major enzymes mediating glucurodination of codeine to C6G. CYP2D6 and CYP3A4 are the major enzymes mediating O-demethylation and N-demethylation of codeine respectively. Morphine and norcodeine are further metabolized by conjugation with glucuronic acid. Morphine and its M6 glucuronide conjugate are pharmacologically active. Whether C6G has pharmacological activity is unknown. Norcodeine and M3 glucuronide conjugate of morphine are generally not considered to be pharmacologically active.

Chlorpheniramine is rapidly and extensively metabolized via demethylation in the liver, forming mono- and didesmethyl derivatives. Oxidative metabolism of chlorpheniramine is catalyzed by CYP2D6.

Elimination

Approximately 90% of the total dose of codeine is excreted through the kidneys, of which approximately 10% is unchanged codeine. Plasma half-life of codeine was observed to be about 5 hours with TUZISTRA XR.

Chlorpheniramine and its metabolites are primarily excreted through the kidneys, with large individual variation. Urinary excretion depends on urine pH and flow rate. Plasma half-life of chlorpheniramine was observed to be about 21 hours with TUZISTRA XR.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Codeine:

Carcinogenicity studies were conducted with codeine. 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 10 and 30 times, respectively, the MRHDD on a mg/m² basis).

Codeine was not mutagenic in the *in vitro* bacterial reverse mutation assay or clastogenic in the *in vitro* Chinese hamster ovary (CHO) cell chromosomal aberration assay.

Fertility studies with codeine have not been conducted.

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 25 and 20 times, respectively, 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 25 and 30 times the MRHDD on a mg/m² basis, respectively.

14 CLINICAL STUDIES

The efficacy of TUZISTRA XR is based on previously established findings of effectiveness of codeine and chlorpheniramine at the proposed doses.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TUZISTRA XR is supplied as a pink to reddish pink, cherry-flavored liquid oral suspension containing codeine polistirex, providing 14.7 mg of codeine (equivalent to 20 mg codeine phosphate), and chlorpheniramine polistirex, providing 2.8 mg chlorpheniramine (equivalent to 4 mg chlorpheniramine maleate) per 5 mL. It is available in bottles of 16 fluid oz. (473 mL) NDC 69442-480-01.

Storage and Handling

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

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

Ensure that patients have an oral dosing dispenser that measures the appropriate volume in milliliters. Counsel patients on how to utilize an oral dosing dispenser and correctly measure the oral suspension as prescribed.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

Overdosage

Advise patients not to increase the dose or dosing frequency of TUZISTRA XR because serious adverse events such as respiratory depression may occur with overdosage [see [Warnings and Precautions \(5.2\)](#); [Overdosage \(10\)](#)].

Dosing

Administer TUZISTRA XR by the oral route only. Pharmacists and prescribers should ensure patients have an oral dosing dispenser that measures the appropriate volume in milliliters. Counsel patients on how to utilize an oral dosing dispenser and correctly measure the oral suspension as prescribed [see [Warnings and Precautions \(5.8\)](#)].

TUZISTRA XR should not be diluted with fluids or mixed together with other drugs.

Concomitant Use of Alcohol and Other Central Nervous System Depressants

Advise patients to avoid the use of alcohol and other central nervous system depressants while taking TUZISTRA XR because additional reduction in mental alertness may occur [see [Warnings and Precautions \(5.5\)](#)].

Activities Requiring Mental Alertness

Caution patients that TUZISTRA XR 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 [see [Warnings and Precautions \(5.5\)](#)].

Controlled Substance Status/Potential for Abuse and Dependence

Caution patients that TUZISTRA XR contains codeine and can produce drug dependence [see [Abuse and Dependence \(9.2, 9.3\)](#)].

PATIENT INFORMATION
TUZISTRA™ XR (two-zis-tra)

(codeine polistirex and chlorpheniramine polistirex) Extended-Release Oral Suspension CIII

What is the most important information I should know about Tuzistra XR extended-release oral suspension?

- **Do not** give Tuzistra XR to a child to treat pain after tonsillectomy or adenoidectomy surgery.
 - When you take Tuzistra XR, some of it changes into morphine in your body.
 - In some children and adults this happens very quickly, and can cause you to stop breathing and cause death due to an overdose.
- Women who breastfeed should talk to their healthcare provider before taking Tuzistra XR.
 - When you take Tuzistra XR, some of it changes into morphine in your body.
 - In some women, this happens very quickly. Codeine and morphine pass into your breast milk. A large amount of morphine can cause your baby to die.
- Call your healthcare provider or get emergency medical help right away if anyone taking Tuzistra XR, or your breastfeeding baby has any of the symptoms listed below:
 - increased sleepiness
 - shallow breathing
 - confusion
 - limpness
 - difficulty breathing
 - your baby has difficulty breastfeeding
- Keep Tuzistra XR 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 Tuzistra XR, get emergency help right away.
- Tuzistra XR can cause serious side effects, including death.
- Take Tuzistra XR exactly as prescribed by your healthcare provider. If you take the wrong dose of Tuzistra XR, you could overdose and die.
- It is especially important when you take Tuzistra XR that you know exactly what dose to take.

What is Tuzistra XR extended-release oral suspension?

Tuzistra XR is a prescription medicine used to treat cough and upper respiratory symptoms you can have with allergies or a common cold. Tuzistra XR is for adults 18 years and older. Tuzistra XR contains 2 medicines, codeine and chlorpheniramine. Codeine is a narcotic cough suppressant. Chlorpheniramine is an antihistamine.

Tuzistra XR is a controlled substance (CIII) because it contains codeine that can be a target for people who abuse prescription medicines or street drugs. Keep your Tuzistra XR in a safe place to protect it from theft. Never give your Tuzistra XR to anyone else even if they have the same symptoms you have. It may harm them or even cause death. Selling or giving away this medicine is against the law.

Tuzistra XR is not for children under 18 years of age. It is not known if Tuzistra XR is safe and effective in children.

Who should not take Tuzistra XR?

Do not give Tuzistra XR to a child to treat pain after tonsillectomy or adenoidectomy surgery.

Do not take Tuzistra XR if you are allergic to any of the ingredients in Tuzistra XR. See the end of this leaflet for a complete list of ingredients in Tuzistra XR.

What should I tell my healthcare provider before taking Tuzistra XR?

Before you take Tuzistra XR, tell your healthcare provider if you:

- have a drug dependence
- have lung or breathing problems
- have had a head injury
- have pain in your stomach (abdomen)
- have prostate problems
- have problems with your urinary tract (urethral stricture)
- plan to have surgery
- abuse alcohol
- have kidney or liver problems
- have thyroid problems, such as hypothyroidism
- are pregnant or plan to become pregnant. It is not known if Tuzistra XR will harm your unborn baby. You and your healthcare provider should decide if you should take Tuzistra XR while you are pregnant.
- are breastfeeding or plan to breastfeed. Tuzistra XR can pass into your milk and may harm your baby. You and your healthcare provider should discuss whether you should take Tuzistra XR or breastfeed. You should not do both.

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

Using Tuzistra XR with certain other medicines may affect each other. Using Tuzistra XR with other medicines can cause

serious side effects.

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)
- take medicines for stomach or intestine problems

How should I take Tuzistra XR?

- Take Tuzistra XR exactly as your healthcare provider tells you.
- **Do not** take more than 20 mL of Tuzistra XR in 24 hours.
- Shake the Tuzistra XR bottle well before you use it.
- Tuzistra XR can be taken with or without food.
- **Do not** mix Tuzistra XR with other fluids or medicines.
- Ask your pharmacist to give you a measuring device to help you measure the correct amount of Tuzistra XR. **Do not use a household teaspoon to measure your medicine. You may accidentally take too much.**
- If you take too much Tuzistra XR, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid doing while taking Tuzistra XR?

- Tuzistra XR can cause you to be drowsy. **Do not** drive a car or use machinery while you take Tuzistra XR until you know how it affects you.
- **Do not** drink alcohol while taking Tuzistra XR. Drinking alcohol can increase your chances of having serious side effects.

What are the possible side effects of Tuzistra XR?

Tuzistra XR may cause serious side effects, including:

- **See “What is the most important information I should know about Tuzistra XR”**
- **decreased breathing** (respiratory depression) which can lead to death. Call your healthcare provider or get emergency treatment right away if you have excessive sleepiness, shallow or slow breathing, or confusion.
- **physical dependence or abuse. Take Tuzistra XR exactly as your healthcare provider tells you to take it.** Stopping Tuzistra XR suddenly could cause withdrawal symptoms.
- **bowel problems** including constipation or stomach pain.

The most common side effects of Tuzistra XR are: nausea, vomiting, blurred vision, double vision, confusion, dizziness, depression, excessive sleepiness, headache, feeling faint, light-headedness, general feeling of discomfort or illness, excitability, nervousness, agitation, and restlessness.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Tuzistra XR. For more information, ask your healthcare provider or pharmacist.

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 Tuzistra XR?

- Store Tuzistra XR in a safe place between 68°F to 77°F (20°C to 25°C).
- Keep Tuzistra XR in a tightly closed container out of the light.
- Safely throw away medicine that is out of date or no longer needed.
- **Keep Tuzistra XR and all medicines out of the reach of children.**

General information about Tuzistra XR:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use Tuzistra XR for a condition for which it was not prescribed. Do not give Tuzistra XR to other people, even if they have the same condition. It may harm them and it is against the law.

This Patient Information Leaflet summarizes the most important information about Tuzistra XR. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Tuzistra XR that is written for healthcare professionals.

For more information about Tuzistra XR extended-release oral suspension call Vernalis Therapeutics, Inc., at 1-855-705-9546 or go to www.vernalistherapeutics.com.

What are the ingredients in Tuzistra XR?

Active Ingredients: codeine polistirex and chlorpheniramine polistirex.

Inactive Ingredients: cherry flavor, citric acid, D&C Red No. 30, ethyl maltol, glycerin, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propyl gallate, propylparaben, purified water, sodium citrate, sodium polystyrene sulfonate, starch, sucrose, triacetin, xanthan gum

Manufactured for: Vernalis Therapeutics, Inc.; Berwyn, PA 19312 vernalistherapeutics.com

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

This Patient Information has been approved by the U.S. Food and Drug Administration.

Date Issued: 04/2015

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NDC 69442-480-01

Tuzistra™XR III
(Codeine Polistirex and Chlorpheniramine Polistirex)
EXTENDED-RELEASE ORAL SUSPENSION

**14.7 mg codeine and
2.8 mg chlorpheniramine
per 5 mL**

Shake Well Before Use
Dispense with an accurate milliliter measuring device
Rx only 16 fl oz (473 mL)

Usual Dosage: See prescribing information.
Pharmacist: Dispense in a tight, light-resistant container with child-resistant closure.
Warning: Keep this and all medications out of the reach of children.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].
Tamper Evident: Do not use product if cap seal is broken or missing.

Distributed by:

Vernalis Therapeutics, Inc.
Berwyn, PA 19312
vernalistherapeutics.com

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



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/s/

LYDIA I GILBERT MCCLAIN
04/30/2015

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