LB8553 Rev. 00 10/2018
TUZISTRA® XR
(codeine polistirex and chlorpheniramine polistirex)
extended-release oral suspension, CIII
Rx only

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

See full prescribing information for complete boxed warning.

- **TUZISTRA XR exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor closely for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or when used in patients at higher risk. (5.2)**
- **Accidental ingestion of TUZISTRA XR, especially by children, can result in a fatal overdose of codeine. (5.2)**
- **Life-threatening respiratory depression and death have occurred in children who received codeine; most cases followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism. (5.3) TUZISTRA XR is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. (4) Avoid the use of TUZISTRA XR in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.**
- **Ensure accuracy when prescribing, dispensing, and administering TUZISTRA XR. Dosing errors can result in accidental overdose and death. (2.1, 5.6)**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex, requiring careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. Avoid the use of TUZISTRA XR in patients who are taking a CYP3A4 inhibitor, CYP3A4 inducer, or 2D6 inhibitor. (5.8, 7.1, 7.2, 7.4)**
- **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. Avoid the use of TUZISTRA XR in patients taking benzodiazepines, other CNS depressants, or alcohol. (5.9, 7.5)**
- **TUZISTRA XR is not recommended for use in pregnant women. Prolonged use of TUZISTRA XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If TUZISTRA XR is used for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.15, 8.1)**

RECENT MAJOR CHANGES

Boxed Warning	6/2018
Indications and Usage (1)	6/2018
Dosage and Administration (2.1, 2.3)	6/2018
Contraindications (4)	8/2017 and 6/2018
Warnings and Precautions (5.3)	8/2017
Warnings and Precautions (5.1, 5.2, 5.4, 5.5, 5.6, 5.8, 5.10, 5.12, 5.13, 5.14, 5.15, 5.16, 5.17)	6/2018

INDICATIONS AND USAGE

TUZISTRA XR is a combination of codeine, an opioid agonist; and chlorpheniramine, a histamine-1 (H_1) receptor antagonist, indicated for the temporary relief of cough and upper respiratory symptoms associated with allergy or the common cold in patients 18 years of age and older. (1)

Important Limitations of Use (1)
- Not indicated for pediatric patients under 18 years of age.
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve TUZISTRA XR for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made.

DOSAGE AND ADMINISTRATION
- Adults 18 years of age and older: 10 mL every 12 hours as needed, not to exceed 2 doses (20 mL) in 24 hours. (2.2)
- Measure TUZISTRA XR with an accurate milliliter measuring device. (2.1, 5)
- Do not increase the dose or dosing frequency. (2.1)
- Prescribe for the shortest duration consistent with treatment goals (2.3)
- Reevaluate patients with unresponsive cough in 5 days or sooner for possible underlying pathology (2.3)
- Reevaluate patient prior to refilling (2.3)

DOSAGE FORMS AND STRENGTHS

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. (3)

CONTRAINDICATIONS
- Children younger than 12 years of age. (4)
- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Concurrent use of monoamine oxidase inhibitor (MAOI) therapy or within the last 14 days. (4)
- Hypersensitivity to codeine or other opiates, chlorpheniramine, or any of the inactive ingredients in TUZISTRA XR. (4)

WARNINGS AND PRECAUTIONS

See Boxed WARNINGS
- Life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients: Monitor closely, particularly during initiation of therapy. (5.5)
- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring mental alertness such as driving or operating machinery. (5.7)
- Risks of use in patients with head injury, impaired consciousness, increased intracranial pressure, or brain tumors: Avoid use. May increase intracranial pressure and obscure the clinical course of head injuries. (5.11)
- Seizures in patients with seizure disorders: Monitor during therapy. (5.12)
- Severe hypotension: Monitor during initiation of therapy. Avoid use in patients with circulatory shock. (5.14)
- Adrenal insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.16)

ADVERSE REACTIONS

Common adverse reactions include: Sedation (somnolence, mental clouding, lethargy), impaired mental and physical performance, lightheadedness, dizziness, headache, dry mouth, nausea, vomiting, constipation, shortness of breath, and sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Aytu BioScience, Inc. at 1-855-298-8246 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Phenytoin: Avoid concomitant use; may increase phenytoin levels. (7.4)
- Serotonergic drugs: Concomitant use may result in serotonin syndrome. Discontinue if serotonin syndrome is suspected. (7.6)
- Muscle relaxants: Avoid concomitant use. (7.8)
- Diuretics: Codeine may reduce the efficacy of diuretics. Monitor for reduced effect. (7.9)
- Anticholinergic drugs: Concomitant use may cause paralytic ileus. (5.10, 7.10)

USE IN SPECIFIC POPULATIONS
- Pregnancy: Avoid use in pregnant women. May cause fetal harm. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)
- 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: 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse
TUZISTRA XR exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Reserve TUZISTRA XR for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made. Assess each patient's risk prior to prescribing TUZISTRA XR, prescribe TUZISTRA XR for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addition or abuse, and refill only after reevaluation of the need for continued treatment. *[see Warnings and Precautions (5.1)]*

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of TUZISTRA XR. Monitor for respiratory depression, especially during initiation of TUZISTRA XR therapy or when used in patients at higher risk *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion
Accidental ingestion of even one dose of TUZISTRA XR, especially by children, can result in a fatal overdose of codeine *[see Warnings and Precautions (5.2)]*.

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children
Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism *[see Warnings and Precautions (5.3)]*. TUZISTRA XR is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*. Avoid the use of TUZISTRA XR in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.

Risk of Medication Errors
Ensure accuracy when prescribing, dispensing, and administering TUZISTRA XR. Dosing errors can result in accidental overdose and death. Always use an accurate milliliter measuring device when measuring and administering TUZISTRA XR *[see Dosage and Administration (2.1), Warnings and Precautions (5.6)]*.

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes
The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex, requiring careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. Avoid the use of TUZISTRA XR in patients who are taking a CYP3A4 inhibitor, CYP3A4 inducer, or 2D6 inhibitor *[see Warnings and Precautions (5.8), Drug Interactions (7.1, 7.2, 7.4)]*.

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. Avoid the use of TUZISTRA XR in patients taking benzodiazepines, other CNS depressants, or alcohol. *[see Warning and Precautions (5.9), Drug Interactions (7.5)]*

Neonatal Opioid Withdrawal Syndrome
TUZISTRA XR is not recommended for use in pregnant women *[see Use in Specific Populations (8.1)]*. Prolonged use of TUZISTRA XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If TUZISTRA XR is used for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.15)]*.

1 INDICATIONS AND USAGE

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

Important Limitations of Use
- Not indicated for pediatric patients under 18 years of age *[see Use in Specific Populations (8.4)]*.
- Contraindicated in pediatric patients under 12 years of age *[see Contraindications (4),Use in Specific Populations (8.4)]*.
- Contraindicated in pediatric patients 12 to 18 years of age after tonsillectomy or adenoidectomy *[see Contraindications (4), Use in Specific Populations (8.4)]*.
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.1)]*, reserve TUZISTRA XR for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Administer TUZISTRA XR by the oral route only. TUZISTRA XR may be administered with or without food.

Always use an accurate milliliter measuring device when administering TUZISTRA XR to ensure that the dose is measured and administered accurately. A household teaspoon is not an accurate measuring device and could lead to overdosage *[see Warnings and Precautions (5.6)]*. For prescriptions where a measuring device is not provided, a pharmacist can provide an appropriate measuring device and can provide instructions for measuring the correct dose. Do not overfill. Rinse the measuring device with water after each use.

Advise patients not to increase the dose or dosing frequency of TUZISTRA XR because serious adverse events such as respiratory depression may occur with overdosage *[see Warnings and Precautions (5.2), Overdosage (10)]*. The dosage of TUZISTRA XR should not be increased if cough fails to respond; an unresponsive cough should be reevaluated for possible underlying pathology *[see Dosage and Administration (2.3), Warnings and Precautions (5.5)]*.

2.2 Recommended Dosage

Adults 18 years of age and older: 10 mL every 12 hours as needed, not to exceed 2 doses (20 mL) in 24 hours.

2.3 Monitoring, Maintenance, and Discontinuation of Therapy

Prescribe TUZISTRA XR for the shortest duration that is consistent with individual patient treatment goals *[see Warnings and Precautions (5.1)]*.

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy *[see Warnings and Precautions (5.2)]*.

Reevaluate patients with unresponsive cough in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease *[see Warnings and Precautions (5.5)]*. If a patient requires a refill, reevaluate the cause of the cough and assess the need for continued treatment with TUZISTRA XR, the relative incidence of adverse reactions, and the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*.

Do not abruptly discontinue TUZISTRA XR in a physically-dependent patient *[see Drug Abuse and Dependence (9.3)]*. When a patient who has been taking TUZISTRA XR regularly and may be physically dependent no longer requires therapy with TUZISTRA XR, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both.

3 DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension: Each 5 mL 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). TUZISTRA XR is a pink to reddish pink, cherry-flavored liquid oral suspension. *[see Description (11)]*

4 CONTRAINDICATIONS

TUZISTRA XR is contraindicated for:
- All children younger than 12 years of age *[see Warnings and Precautions (5.2, 5.3),Use in Specific Populations (8.4)]*.
- Postoperative pain management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.2,5.3)]*.

TUZISTRA XR is also contraindicated in patients with:
- Significant respiratory depression *[see Warnings and Precautions (5.2)]*.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.5)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.10)]*.
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within 14 days *[see Warnings and Precautions (5.13), Drug Interactions (7.7)]*.
- Hypersensitivity to codeine, chlorpheniramine, or any of the inactive ingredients in TUZISTRA XR *[see Adverse Reactions (6)]*. Persons known to be hypersensitive to certain other opioids may exhibit cross-reactivity to codeine.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

TUZISTRA XR contains codeine, a Schedule III controlled substance. As an opioid, TUZISTRA XR exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*, which can lead to overdose and death *[see Overdosage (10)]*. **Reserve TUZISTRA XR for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made. Assess each patient's risk prior to prescribing TUZISTRA XR, prescribe TUZISTRA XR for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addiction or abuse, and refill only after reevaluation of the need for continued treatment.**

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

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing TUZISTRA XR. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, including codeine, one of the active ingredients in TUZISTRA XR. Codeine produces dose-related respiratory depression by directly acting on the brain stem respiratory center that controls respiratory rhythm and may produce irregular and periodic breathing. Codeine is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to an increased exposure to the active metabolite morphine *[see Warnings and Precautions (5.3)]*. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression includes discontinuation of TUZISTRA XR, close observation, supportive measures, and use of opioid antagonists (e.g. naloxone), depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of TUZISTRA XR, the risk is greatest during the initiation of therapy, when TUZISTRA XR is used concomitantly with other drugs that may cause respiratory depression *[see Warnings and Precautions (5.9)]*, in patients with chronic pulmonary disease or decreased respiratory reserve, and in patients with altered pharmacokinetics or altered clearance (e.g. elderly, cachectic, or debilitated patients) *[see Warnings and Precautions (5.5)]*.

To reduce the risk of respiratory depression, proper dosing of TUZISTRA XR is essential *[see Dosage and Administration (2.1), Warnings and Precautions (5.6)]*. Monitor patients closely, especially within the first 24-72 hours of initiating therapy or when used in patients at higher risk.

Overdose of codeine in adults has been associated with fatal respiratory depression, and the use of codeine in children younger than 12 years of age has been associated with fatal respiratory depression when used as recommended *[see Warnings and Precautions (5.3)]*. Accidental ingestion of even one dose of TUZISTRA XR, especially by children, can result in respiratory depression and death.

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

Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:
- TUZISTRA XR is contraindicated in all children younger than 12 years of age *[see Contraindications (4)]*.
- TUZISTRA XR is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.
- Avoid the use of TUZISTRA XR in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. *[see Warnings and Precautions (5.9),Use in Specific Populations (8.4)]*
- Healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose *[see Warnings and Precautions (5.1), Overdosage (10)]*.

Lactation

At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with TUZISTRA XR *[see Use in Specific Populations (8.2)]*.

CYP2D6 Genetic Variability: Ultra-Rapid Metabolizers

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain /ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) *[see Overdosage (10)]*. Therefore, individuals who are ultra-rapid metabolizers should not use TUZISTRA XR.

5.4 Risks with Use in Pediatric Populations

Children are particularly sensitive to the respiratory depressant effects of codeine *[see Warnings and Precautions (5.2, 5.3)]*. Because of the risk of life-threatening respiratory depression and death, TUZISTRA XR is contraindicated in children less than 12 years of age, and in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

Use of TUZISTRA XR in children also exposes them to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*, which can lead to overdose and death *[see Warnings and Precautions (5.1), Overdosage (10)]*. Because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks of use of codeine in pediatric patients, TUZISTRA XR is not indicated for use in patients younger than 18 years of age *[see Indications (1), Use in Specific Populations (8.4)]*

5.5 Risks with Use in Other At-Risk Populations

Unresponsive Cough

The dosage of TUZISTRA XR should not be increased if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease *[see Dosage and Administration (2.3)]*.

Asthma and Other Pulmonary Disease

The use of TUZISTRA XR in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated *[see Contraindications (4)]*.

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

TUZISTRA XR-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of TUZISTRA XR *[see Warnings and Precautions (5.2)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

Because of the risk of respiratory depression, avoid the use of opioid antitussives, including TUZISTRA XR in patients with compromised respiratory function, patients at risk of respiratory failure, and in elderly, cachectic, or debilitated patients. If TUZISTRA XR is prescribed, monitor such patients closely, particularly when initiating TUZISTRA XR and when TUZISTRA XR is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.9)]*.

5.6 Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. To reduce the risk of overdose and respiratory depression, ensure that the dose of TUZISTRA XR is communicated clearly and dispensed accurately *[see Dosage and Administration (2.1)]*.

Advise patients to always use an accurate milliliter measuring device when measuring and administering TUZISTRA XR. Inform patients that household teaspoon is not an accurate measuring device and such use could lead to overdosage and serious adverse reactions *[see Overdosage (10)]*. For prescriptions where a measuring device is not provided, a pharmacist can provide an appropriate calibrated measuring device and can provide instructions for measuring the correct dose.

5.7 Activities Requiring Mental Alertness: Risks of Driving and Operating Machinery

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. Avoid concurrent use of TUZISTRA XR with alcohol or other central nervous system depressants because additional impairment of central nervous system performance may occur *[see Warnings and Precautions (5.9)]*.

5.8 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

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

Cytochrome P450 3A4 Interaction

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

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

Avoid the use of TUZISTRA XR in patients who are taking a CYP3A4 inhibitor or CYP3A4 inducer. If concomitant use of TUZISTRA XR with inhibitors and inducers of CYP3A4 is necessary, monitor patients for signs and symptoms that may reflect opioid toxicity and opioid withdrawal *[see Drug Interactions (7.1, 7.2)]*.

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

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

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

Avoid the use of TUZISTRA XR in patients who are taking a CYP2D6 inhibitor. If concomitant use of TUZISTRA XR with inhibitors of CYP2D6 is necessary, monitor patients for signs and symptoms that may reflect opioid toxicity and opioid withdrawal *[see Drug Interactions (7.4)]*.

5.9 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Concomitant use of opioids, including TUZISTRA XR, 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 (7.5)]*.

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 TUZISTRA XR is used with benzodiazepines, alcohol, or other CNS depressants *[see Patient Counseling Information (17)]*.

5.10 Risks of Use in Patients with Gastrointestinal Conditions

TUZISTRA XR is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus *[see Contraindications (4)]*. The use of codeine in TUZISTRA XR may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

The concurrent use of anticholinergics with TUZISTRA XR may produce paralytic ileus *[see Drug Interactions (7.10)]*.

The codeine in TUZISTRA XR may result in constipation or obstructive bowel disease, especially in patients with underlying intestinal motility disorders. Use with caution in patients with underlying intestinal motility disorders.

The codeine in TUZISTRA XR may cause spasm of the sphincter of Oddi, resulting in an increase in biliary tract pressure. Opioids may cause increases in serum amylase *[see Warnings and Precautions (5.17)]*. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

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

Avoid the use of TUZISTRA XR in patients with head injury, intracranial lesions, or a pre-existing increase in intracranial pressure. In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), TUZISTRA XR may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Furthermore, opioids produce adverse reactions that may obscure the clinical course of patients with head injuries.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The codeine and chlorpheniramine in TUZISTRA XR may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during TUZISTRA XR therapy.

5.13 Co-administration with Monoamine Oxidase Inhibitors (MAOIs)

Concurrent use of TUZISTRA XR is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such therapy *[see Contraindications (4)]*. MAOIs may potentiate the effects of morphine, codeine's active metabolite, including respiratory depression, coma, and confusion MAOIs *[see Drug Interactions (7.7)].*

5.14 Severe Hypotension

TUZISTRA XR may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7.5)]*. Monitor these patients for signs of hypotension after initiating TUZISTRA XR.

In patients with circulatory shock, TUZISTRA XR may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of TUZISTRA XR in patients with circulatory shock.

5.15 Neonatal Opioid Withdrawal Syndrome

TUZISTRA XR is not recommended for use in pregnant women. Prolonged use of TUZISTRA XR during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.16 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.17 Drug/Laboratory Test Interactions

Because opioid agonists may increase biliary tract pressure, with resultant increase in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after administration of a dose of TUZISTRA XR.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:
- Addiction, abuse, and misuse *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.3)]*
- Life-threatening respiratory depression *[see Warnings and Precautions (5.2, 5.3, 5.4, 5.5, 5.9), Overdosage (10)]*
- Ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children *[see Warnings and Precautions (5.3)]*
- Accidental overdose and death due to medication errors *[see Warnings and Precautions (5.6)]*
- Decreased mental alertness with impaired mental and/or physical abilities *[see Warnings and Precautions (5.7)]*
- Interactions with benzodiazepines and other CNS depressants *[see Warnings and Precautions (5.9)]*
- Paralytic ileus, gastrointestinal adverse reactions *[see Warnings and Precautions (5.10)]*
- Increased intracranial pressure *[see Warnings and Precautions (5.11)]*
- Obscured clinical course in patients with head injuries *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Interactions with MAOI *[see Warnings and Precautions (5.13)]*
- Severe hypotension *[see Warnings and Precautions (5.14)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.15)]*
- Adrenal insufficiency *[see Warnings and Precautions (5.16)]*

The following adverse reactions have been identified during clinical studies, in the literature, or during post-approval use of codeine and/or chlorpheniramine. 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.

The most common adverse reactions to TUZISTRA XR include: Sedation (somnolence, mental clouding, lethargy), impaired mental and physical performance, lightheadedness, dizziness, headache, dry mouth, nausea, vomiting, constipation, shortness of breath, and sweating.

Other reactions include:

Anaphylaxis: Anaphylaxis has been reported with codeine, one of the ingredients in TUZISTRA XR.

Body as a whole: Coma, death, fatigue, falling injuries, lethargy.

Cardiovascular: Peripheral edema, increased blood pressure, decreased blood pressure, tachycardia, chest pain, palpitation, syncope, orthostatic hypotension, prolonged QT interval, hot flush.

Central Nervous System: Ataxia, facial dyskinesia, insomnia, increased intracranial pressure, migraine, seizure, tremor, tinnitus, vertigo.

Dermatologic: Flushing, hyperhidrosis, pruritus, rash.

Endocrine/Metabolic: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs. Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

Gastrointestinal: Abdominal pain, bowel obstruction, decreased appetite, diarrhea, difficulty swallowing, GERD, indigestion, pancreatitis, paralytic ileus, biliary tract spasm (spasm of the sphincter of Oddi).

Genitourinary: Urinary tract infection, ureteral spasm, spasm of vesicle sphincters, urinary retention.

Hematologic: Agranulocytosis, aplastic anemia, and thrombocytopenia have been reported.

Laboratory: Increases in serum amylase.

Musculoskeletal: Arthralgia, backache, muscle spasm.

Ophthalmic: Blurred vision, diplopia, miosis (constricted pupils), visual disturbances.

Psychiatric: Agitation, anxiety, confusion, fear, dysphoria, depression, hallucinations.

Reproductive: Hypogonadism, infertility.

Respiratory: Bronchitis, cough, dry nose, dry throat, dyspnea, nasal congestion, nasopharyngitis, respiratory depression, sinusitis, thickening of bronchial secretions, tightness of chest and wheezing, upper respiratory tract infection.

Other: Drug abuse, drug dependence, opioid withdrawal syndrome.

7 DRUG INTERACTIONS

No specific drug interaction studies have been conducted with TUZISTRA XR.

7.1 Inhibitors of CYP3A4

The concomitant use of TUZISTRA XR with CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), or protease inhibitors (e.g., ritonavir), may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of TUZISTRA XR is achieved *[see Warnings and Precautions (5.8)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower codeine levels, greater norcodeine levels, and less metabolism via CYP2D6 with resultant lower morphine levels *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to codeine.

Avoid the use of TUZISTRA XR while taking a CYP3A4 inhibitor. If concomitant use is necessary, monitor patients for respiratory depression and sedation at frequent intervals.

7.2 CYP3A4 Inducers

The concomitant use of TUZISTRA XR and CYP3A4 inducers, such as rifampin, carbamazepine, or phenytoin, can result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence *[see Warnings and Precautions (5.8)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, codeine plasma concentrations may increase with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

Avoid the use of TUZISTRA XR in patients who are taking CYP3A4 inducers. If concomitant use of a CYP3A4 inducer is necessary, follow the patient for reduced efficacy.

7.3 Phenytoin

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. Avoid the use of TUZISTRA XR while taking phenytoin.

7.4 Inhibitors of CYP2D6

Codeine is metabolized by CYP2D6 to form morphine. The concomitant use of TUZISTRA XR and CYP2D6 inhibitors, such as paroxetine, fluoxetine, bupropion, or quinidine, can increase the plasma concentration of codeine, but can decrease the plasma concentration of active metabolite morphine, which could result in reduced efficacy *[see Clinical Pharmacology (12.3)]*.

After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease but the active metabolite morphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression *[see Clinical Pharmacology (12.3)]*.

Avoid the use of TUZISTRA XR in patients who are taking inhibitors of CYP2D6.

7.5 Benzodiazepines, and Other CNS Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. Avoid the use of TUZISTRA XR in patients who are taking benzodiazepines or other CNS depressants *[see Warnings and Precautions (5.9)]*.

7.6 Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation. Discontinue TUZISTRA XR if serotonin syndrome is suspected.

7.7 Monoamine Oxidase Inhibitors (MAOIs)

TUZISTRA XR is contraindicated in patients who are taking MAOIs (i.e., certain drugs used for depression, psychiatric or emotional conditions, or Parkinson's disease) or have taken MAOIs within 14 days *[see Contraindications (4)]*.

MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.13)]*.

7.8 Muscle Relaxants

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

7.9 Diuretics

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

7.10 Anticholinergic Drugs

The concomitant use of anticholinergic drugs with TUZISTRA XR may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus *[see Warnings and Precautions (5.10)]*. Monitor patients for signs of urinary retention or reduced gastric motility when TUZISTRA XR is used concomitantly with anticholinergic drugs.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TUZISTRA XR is not recommended for use in pregnant women, including during or immediately prior to labor.

Prolonged use of opioids during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.15), Clinical Considerations]*.

There are no available data with TUZISTRA XR use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. Published studies with codeine have reported inconsistent findings and have important methodological limitations *(see Data)*. There are reports of respiratory depression when codeine is used during labor and delivery *(see Clinical Considerations)*.

Reproductive toxicity studies have not been conducted with TUZISTRA XR; however, studies are available with individual active ingredients *(see Data)*.

In animal reproduction studies, codeine administered by the oral route to pregnant rats during the period of organogenesis increased resorptions and decreased fetal weights at a dose approximately 20 times the maximum recommended human dose (MRHD) in the presence of maternal toxicity *(see Data)*.

Chlorpheniramine administered by the oral route to mice throughout pregnancy was embryolethal at a dose approximately 9 times the MRHD and decreased postnatal survival when dosing was continued after parturition. Chlorpheniramine administered by the oral route to male and female rats prior to mating produced embryolethality at a dose approximately 9 times the MRHD *(see Data)*.

Based on the animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.15)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Opioids, including TUZISTRA XR, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioids during labor for signs of excess sedation and respiratory depression.

Data

Human Data

Codeine

Published data from case-control and observational studies on codeine use during pregnancy are inconsistent in their findings. Some studies of codeine exposure showed an increased risk of overall congenital malformations while others did not. An increased risk of specific malformations with codeine exposure such as respiratory malformations, spina bifida and congenital heart defects were reported in some studies. Most of the studies, both positive and negative, were limited by small sample size, recall bias and lack of information regarding dose and timing of exposure.

Chlorpheniramine

The majority of studies examining the use of chlorpheniramine in pregnancy did not find an association with an increased risk of congenital anomalies. In the few studies reporting an association, there was no consistent pattern of malformations noted.

Animal Data

Reproductive toxicity studies have not been conducted with TUZISTRA XR; however, studies are available with individual active ingredients.

Codeine

In an embryofetal development study in pregnant rats dosed throughout the period of organogenesis, codeine increased resorptions and decreased fetal weights at a dose approximately 20 times the MRHD (on a mg/m² basis with a maternal oral dose of 120 mg/kg/day); however, these effects occurred in the presence of maternal toxicity. In embryofetal development studies with pregnant rabbits and mice dosed throughout the period of organogenesis, codeine produced no adverse developmental effects at doses approximately 10 and 50 times, respectively, the MRHD (on a mg/m² basis with maternal oral doses of 30 mg/kg/day in rabbits and 600 mg/kg/day in mice).

Chlorpheniramine

In embryofetal development studies with pregnant rats and rabbits dosed throughout the period of organogenesis, chlorpheniramine produced no adverse developmental effects at oral doses up to approximately 35 and 45 times, respectively, the MRHD on a mg/m² basis. However, in a reproduction study with pregnant mice dosed throughout pregnancy, chlorpheniramine produced embryolethality at a dose approximately 9 times the MRHD (on a mg/m² basis with a maternal oral dose of 20 mg/kg/day) and decreased postnatal survival when dosing was continued after parturition. In a fertility and reproducti on study with male and female rats dosed prior to mating, chlorpheniramine produced embryolethality at a dose approximately 9 times the MRHD (on a mg/m² basis with an oral parental dose of 10 mg/kg/day).

8.2 Lactation

Risk Summary

Because of the potential for serious adverse reactions, including excess sedation, respiratory depression, and death in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with TUZISTRA XR *[see Warnings and Precautions (5.3)]*.

There are no data on the presence of TUZISTRA XR in human milk, the effects of TUZISTRA XR on the breastfed infant, or the effects of TUZISTRA XR on milk production; however, data are available with codeine and chlorpheniramine.

Codeine

Codeine and its active metabolite, morphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression and death (in one infant) in infants exposed to codeine via breast milk. Women who are ultra-rapid metabolizers of codeine achieve higher than expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous in their breastfed infants. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. There is no information on the effects of the codeine on milk production.

Chlorpheniramine

Chlorpheniramine is present in human milk. Chlorpheniramine has not been reported to cause effects on the breastfed infant. The published literature suggests that chlorpheniramine may decrease milk production based on its anticholinergic effects. *(see Clinical Considerations)*

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TUZISTRA® XR
(codeine polistirex and chlorpheniramine polistirex)
extended-release oral suspension, CIII
Rx only

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(codeine polistirex and chlorpheniramine polistirex)
extended-release oral suspension, CIII
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Clinical Considerations

Infants exposed to TUZISTRA XR through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid is stopped, or when breastfeeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids, such as codeine, a component of TUZISTRA XR, may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

8.4 Pediatric Use

TUZISTRA XR is not indicated for use in patients younger than 18 years of age because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks for use of codeine in these patients *[see Indications (1), Warnings and Precautions (5.4)]*.

Life-threatening respiratory depression and death have occurred in children who received codeine *[see Warnings and Precautions (5.2)]*. In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine.

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

- TUZISTRA XR is contraindicated for all children younger than 12 years of age *[see Contraindications (4)]*.
- TUZISTRA XR is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.
- Avoid the use of TUZISTRA XR in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression *[see Warnings and Precautions (5.3)]*.

8.5 Geriatric Use

Clinical studies have not been conducted with TUZISTRA XR in geriatric populations.

Use caution when considering the use of TUZISTRA XR in patients 65 years of age or older. Elderly patients may have increased sensitivity to codeine; greater frequency of decreased hepatic, renal, or cardiac function; or concomitant disease or other drug therapy *[see Warnings and Precautions (5.5)]*.

Respiratory depression is the chief risk for elderly patients treated with opioids, including TUZISTRA XR. Respiratory depression has occurred after large initial doses of opioids were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration *[see Warnings and Precautions (5.5, 5.9)]*.

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

8.6 Renal Impairment

The pharmacokinetics of TUZISTRA XR has not been characterized in patients with renal impairment. Codeine pharmacokinetics may be altered in patients with renal failure. Clearance may be decreased and the metabolites may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Chlorpheniramine is 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 chlorpheniramine. Therefore, TUZISTRA XR should be used with caution in patients with severe impairment of renal function, and patients should be monitored closely for signs of codeine toxicity (respiratory depression, sedation, and hypotension) and chlorpheniramine toxicity.

8.7 Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of TUZISTRA XR in this patient population are unknown. Chlorpheniramine is extensively metabolized by 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 chlorpheniramine. Therefore, TUZISTRA XR should be used with caution in patients with severe impairment of hepatic function, and patients should be monitored closely for signs of codeine toxicity (respiratory depression, sedation, and hypotension) and chlorpheniramine toxicity.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TUZISTRA XR contains codeine, a Schedule III controlled substance.

9.2 Abuse

Codeine

TUZISTRA XR contains codeine, a substance with a high potential for abuse similar to other opioids including morphine and codeine. TUZISTRA XR can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic and antitussive products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

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

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

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

TUZISTRA XR, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of TUZISTRA XR

TUZISTRA XR is for oral use only. Abuse of TUZISTRA XR poses a risk of overdose and death. The risk is increased with concurrent use of TUZISTRA XR with alcohol and other central nervous system depressants *[see Warnings and Precautions (5.9)]*.

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

9.3 Dependence

Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, TUZISTRA XR should be prescribed and administered for the shortest duration that is consistent with individual patient treatment goals and patients should be reevaluated prior to refills *[see Dosage and Administration (2.3), Warnings and Precautions (5.1)]*.

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

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

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Codeine

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

Codeine may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Chlorpheniramine

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

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

Toxic psychosis, a possible class effect from overdose of sedating antihistamines, has been reported.

Treatment of Overdose

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

The opioid antagonists, naloxone and nalmefene, are specific antidotes for respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to codeine overdose, administer an opioid antagonist. An antagonist should not be administered in the absence of clinically significant respiratory depression. Because the duration of opioid reversal is expected to be less than the duration of action of codeine in TUZISTRA XR, carefully monitor the patient until spontaneous respiration is reliably reestablished. TUZISTRA XR will continue to release codeine and add to the codeine load for 12 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

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 suspension contains codeine, an opioid agonist; and chlorpheniramine, a histamine-1 (H_1) receptor antagonist.

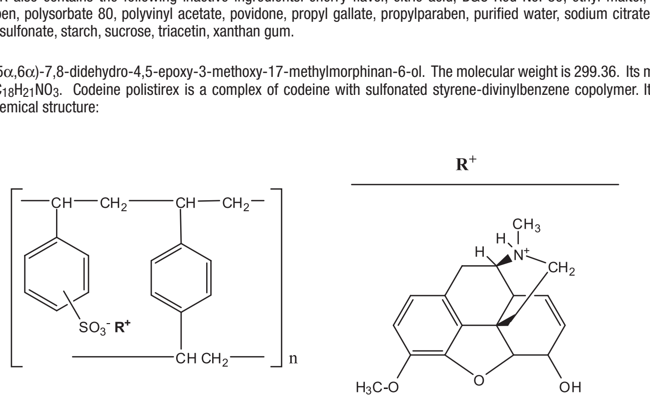
Each 5 mL of TUZISTRA XR contains 14.7 mg of codeine and 2.8 mg of chlorpheniramine bound to sulfonated styrene-divinylbenzene copolymer (polistirex) for oral administration.

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

TUZISTRA XR also 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.

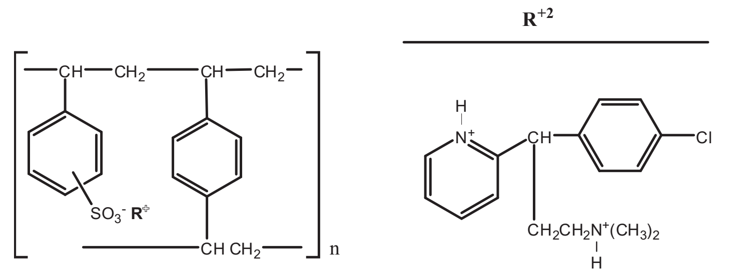
Codeine

Codeine is (5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol. The molecular weight is 299.36. Its molecular formula is $C_{18}H_{21}NO_3$. Codeine polistirex is a complex of codeine with sulfonated styrene-divinylbenzene copolymer. It has the following chemical structure:



Chlorpheniramine

Chlorpheniramine is γ-(4-chlorophenyl)-N, N-dimethyl-2-pyridinepropanamine, has the following molecular formula, $C_{16}H_{19}ClN_2$, and a molecular weight of 274.80. Chlorpheniramine polistirex is a complex of chlorpheniramine with sulfonated styrene-divinylbenzene copolymer. It has the following chemical structure:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Codeine

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

Chlorpheniramine

Chlorpheniramine is a propylamine derivative antihistamine (H_1-receptor antagonist) of the alkylamine class that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

12.2 Pharmacodynamics

Codeine

Effects on the Central Nervous System

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

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

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Codeine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

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

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

Effects on the Immune System

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

Concentration–Adverse Reaction Relationships

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

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. Codeine has low plasma protein binding with about 7 to 25% of codeine 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.

Elimination

Metabolism

Codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide (about 70 to 80%), by O-demethylation to morphine (about 5 to 10%), and by N-demethylation to norcodeine (about 10%). UDP-glucuronosyltransferase (UGT) 2B7 and 2B4 are the major enzymes mediating glucuronidation of codeine to C6G. Cytochrome P450 2D6 is the major enzyme responsible for conversion of codeine to morphine and P450 3A4 is the major enzyme mediating conversion of codeine to norcodeine. Morphine and norcodeine are further metabolized by conjugation with glucuronic acid. The glucuronide metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). 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 cytochrome P-450 2D6.

Excretion

Approximately 90% of the total dose of codeine is excreted through the kidneys, of which approximately 10% is unchanged codeine. The mean plasma half-life of codeine measured in a single-dose study with TUZISTRA XR was approximately 5 hours. Chlorpheniramine and its metabolites are primarily excreted through the kidneys, with large individual variation. Urinary excretion depends on urine pH and flow rate. The mean plasma half-life of chlorpheniramine measured in a single-dose study with TUZISTRA XR was approximately 21 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

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

Codeine

Carcinogenicity studies were conducted with codeine. Two-year studies in F344/N rats and B6C3F1 mice were conducted to assess the carcinogenic potential of codeine. No evidence of tumorigenicity was observed in male and female rats at codeine dietary doses up to 70 and 80 mg/kg/day (approximately equivalent to 10 and 15 times, the MRHD on a mg/m² basis, respectively). No evidence of tumorigenicity was observed in male and female mice at codeine dietary doses up to 400 mg/kg/day (approximately equivalent to 35 times the MRHD 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

Carcinogenicity studies were conducted with chlorpheniramine maleate. Two-year studies in F344/N rats and B6C3F1 mice were conducted to assess the carcinogenic potential of chlorpheniramine. No evidence of tumorigenicity was observed in male and female rats at chlorpheniramine oral doses up to 30 and 60 mg/kg/day for 5 days/week (approximately equivalent to 25 and 50 times the MRHD on a mg/m² basis, respectively). No evidence of tumorigenicity was observed in male and female mice at chlorpheniramine oral doses up to 50 and 200 mg/kg/day for 5 days/week (approximately equivalent to 20 and 85 times the MRHD on a mg/m² basis, respectively).

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* Chinese hamster ovary (CHO) cell chromosomal aberration assay.

Chlorpheniramine maleate had no effects on fertility in rats and rabbits at oral doses approximately 35 and 45 times the MRHD on a mg/m² basis, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 69654-480-01.

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

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse

Inform patients that the use of TUZISTRA XR, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share TUZISTRA XR with others and to take steps to protect TUZISTRA XR from theft or misuse.

Important Dosing and Administration Instructions

Instruct patients how to measure and take the correct dose of TUZISTRA XR. Advise patients 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. Advise patients to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose *[see Dosage and Administration (2.1) and Warnings and Precautions (5.6)]*. 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)]*.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting TUZISTRA XR and that it can occur even at recommended dosages *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store TUZISTRA XR securely and to properly dispose of unused TUZISTRA XR in accordance with the local state guidelines and/or regulations.

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

Advise caregivers that TUZISTRA XR is not indicated for pediatric patients under 18 years of age and is contraindicated in all children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

Activities Requiring Mental Alertness

Advise patients to avoid engaging in hazardous tasks that require mental alertness and motor coordination such as operating machinery or driving a motor vehicle as TUZISTRA XR may produce marked drowsiness *[see Warnings and Precautions (5.7)]*.

Interactions with Benzodiazepines and Other Central Nervous System Depressants, Including Alcohol

Inform patients and caregivers that potentially fatal additive effects may occur if TUZISTRA XR is used with benzodiazepines or other CNS depressants, including alcohol. Advise patients to avoid concomitant use of TUZISTRA XR with benzodiazepines or other CNS depressants and to not use alcohol while taking TUZISTRA XR *[see Warnings and Precautions (5.9), Drug Interactions (7.5)]*.

Constipation

Advise patients of the potential for severe constipation *[see Warnings and Precautions (5.10), Adverse Reactions (6)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in TUZISTRA XR. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

MAOI Interaction

Inform patients not to take TUZISTRA XR while using or within 14 days of stopping any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking TUZISTRA XR *[see Warnings and Precautions (5.13), Drug Interactions (7.7)]*.

Hypotension

Inform patients that TUZISTRA XR may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.14)]*.

Pregnancy

Advise patients that use of TUZISTRA XR is not recommended during pregnancy *[see Use in Specific Populations (8.1)]*.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of TUZISTRA XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.15), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that TUZISTRA XR can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise women that breastfeeding is not recommended during treatment with TUZISTRA XR *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that chronic use of opioids, such as codeine, a component of TUZISTRA XR, may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Adrenal Insufficiency

Inform patients that TUZISTRA XR could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.16)]*.

Serotonin Syndrome

Inform patients that TUZISTRA XR could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications. *[see Adverse Reactions (6), Drug Interactions (7.6)]*.

Disposal of Unused TUZISTRA XR

Advise patients to properly dispose of unused TUZISTRA XR. Advise patients to throw the drug in the household trash following these steps. 1) Remove them from their original containers and mix them with an undesirable substance, such as used coffee grounds or kitty litter (this makes the drug less appealing to children and pets, and unrecognizable to people who may intentionally go through the trash seeking drugs). 2) Place the mixture in a sealable bag, empty can, or other container to prevent the drug from leaking or breaking out of a garbage bag, or to dispose of in accordance with local state guidelines and/or regulations.

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

Aytu BioScience, Inc.
373 Inverness Parkway, Suite 206
Englewood, CO 80112

LiquiXR is a registered trademark of Tris Pharma, Inc.

LB8553 Rev.00 Revised: October 2018

Medication Guide
TUZISTRA® XR (Two-zis-tra)
(codeine polistirex and chlorpheniramine polistirex)
extended-release oral suspension, C-III

What is the most important information I should know about TUZISTRA XR?
TUZISTRA XR is not for children under 18 years of age.
TUZISTRA XR can cause serious side effects, including:

- **Addiction, abuse and misuse**. Taking TUZISTRA XR or other medicines that contain an opioid can cause addiction, abuse, and misuse, which can lead to overdose and death. This can happen even if you take TUZISTRA XR exactly as prescribed by your healthcare provider. Your risk of addiction, abuse, and misuse is increased if you or a family member has a history of drug or alcohol abuse or addiction, or mental health problems.
  - **Do not** share your TUZISTRA XR with other people.
  - Keep TUZISTRA XR in a safe place away from children.
- **Life-threatening breathing problems (respiratory depression)**. TUZISTRA XR can cause breathing problems (respiratory depression) that can happen at any time during treatment and can lead to death. Your risk of breathing problems is greatest when you first start taking TUZISTRA XR, are taking other medicines that can cause breathing problems, have certain lung problems, are elderly or have certain other health problems. **Children are at higher risk for respiratory depression**. Breathing problems can happen even if you take TUZISTRA XR exactly as prescribed by your healthcare provider.
  Call your healthcare provider or get emergency medical help right away if anyone taking TUZISTRA XR has any of the symptoms below:
- increased sleepiness
- confusion
- difficulty breathing
- shallow breathing
- limpness

  Keep TUZISTRA XR in a safe place away from children. Accidental use of even 1 dose of TUZISTRA XR, especially by a child, is a medical emergency and can cause breathing problems (respiratory depression) which can lead to death. If a child accidentally takes TUZISTRA XR, get emergency help right away.
- **Overdose and death due to medicine dosing errors**. Overdose and death can happen if you measure the wrong dose of TUZISTRA XR. Always use an accurate milliliter (mL) measuring device to measure the correct amount of TUZISTRA XR. **Do not** use a household teaspoon to measure your medicine. You may accidentally take too much. You can ask your pharmacist for the measuring device you should use and how to measure the correct dose.
- **Breathing problems (respiratory depression) that can lead to death and opioid withdrawal** can happen if you start taking or stop taking other medicines while taking TUZISTRA XR, including:
- certain antibiotics
- certain medicines to treat a fungal infection
- certain medicines to treat Human Immunodeficiency Virus (HIV)-1 infection, Acquired Immune Deficiency Syndrome (AIDS), or Hepatitis C
- rifampin
- carbamazepine
- phenytoin
- **Severe drowsiness, breathing problems (respiratory depression), coma, and death** can happen in adults and children who take TUZISTRA XR with benzodiazepines, or other central nervous system depressants, including alcohol.
  - **Do not** take any benzodiazepines or medicines that can cause drowsiness or sleepiness during treatment with Tuzistra XR. Ask your healthcare provider for a list of these medicines if you are not sure.
  - **Do not** drink alcohol during treatment with TUZISTRA XR.
- **Opioid withdrawal in a newborn**. Use of TUZISTRA XR during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. You should not take TUZISTRA XR if you are pregnant. Tell your healthcare provider right away if you are pregnant or think you may be pregnant.

What is TUZISTRA XR?

- TUZISTRA XR is a prescription medicine used in adults to treat cough and upper respiratory symptoms that you can have with allergies or a common cold. TUZISTRA XR contains 2 medicines, codeine and chlorpheniramine. Codeine is an opioid (narcotic) cough suppressant. Chlorpheniramine is an antihistamine.
- **TUZISTRA XR is a federal controlled substance (C-III) because it contains codeine that can be abused or lead to dependence**. Keep TUZISTRA XR in a safe place to prevent misuse and abuse. Selling or giving away TUZISTRA XR 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.

Who should not take TUZISTRA XR?
TUZISTRA XR is not for children under 18 years of age. See **"What is the most important information I should know about TUZISTRA XR?"**
Do not take TUZISTRA XR if you:

- have severe breathing problems (respiratory depression). See **"What is the most important information I should know about TUZISTRA XR?"**
- have a blockage (obstruction) in your bowel such as a paralytic ileus.
- take a medicine for depression called a Monoamine Oxidase Inhibitor (MAOI).
  - **Do not** take an MAOI within 14 days after you stop taking TUZISTRA XR.
  - **Do not** start taking TUZISTRA XR if you stopped taking an MAOI in the last 14 days.
- are allergic to codeine, chlorpheniramine, or any of the ingredients in TUZISTRA XR. See the end of this Medication Guide for a complete list of ingredients in TUZISTRA XR. You may have an increased risk of an allergic reaction to TUZISTRA XR if you are allergic to certain other opioid medicines.

Ask your healthcare provider if you have any questions about this information.

Before you take TUZISTRA XR, tell your healthcare provider about all your medical conditions, including if you:

- have a drug addiction
- have lung or breathing problems
- have a fever and are coughing up mucus
- have had a recent head injury
- have had brain tumor or other brain problems
- have or have had seizures
- have pain in your stomach-area (abdomen)
- have constipation or other bowel problems
- have bile duct or pancreas problems
- have prostate problems
- have problems with your urinary tract or difficulty urinating
- have kidney or liver problems
- have adrenal gland problems
- have low blood pressure (hypotension)
- plan to have surgery
- are pregnant or plan to become pregnant. TUZISTRA XR can harm your unborn baby. See **"What is the most important information I should know about TUZISTRA XR?"**
- are breastfeeding or plan to breastfeed. Codeine and chlorpheniramine pass into your breast milk and can cause serious side effects in your baby including increased sleepiness, breathing problems (respiratory depression), and death. You and your healthcare provider should decide if you will take TUZISTRA XR or breastfeed. You should not do both. See **"What should I avoid while taking TUZISTRA XR?"**
- plan to have children. TUZISTRA XR may affect the ability to have a child in females and males (fertility problems). It is not known if these fertility problems will be reversible, even after you stop taking TUZISTRA XR. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Taking TUZISTRA XR with certain other medicines can cause side effects or affect how well TUZISTRA XR or the other medicines work. Do not start or stop taking other medicines without talking to your healthcare provider.
Especially tell your healthcare provider if you:

- See **"What is the most important information I should know about TUZISTRA XR?"**
- take pain medicines such as opioids (narcotics).
- take cold or allergy medicines that contain antihistamines or cough suppressants.
- drink alcohol.
- take muscle relaxants.
- take certain medicines used to treat mood, anxiety, psychotic or thought disorders, or depression, including monoamine oxidase inhibitors (MAOIs), tricyclics, selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), or antipsychotics.
- take medicines to lower your blood pressure.
- water pills (diuretics).
- take medicines called "anticholinergics" used to treat health problems such as asthma, chronic obstructive pulmonary disease (COPD), or stomach problems.
- take a medicine called "phenytoin" used to treat seizures or epilepsy.

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

How should I take TUZISTRA XR?

- See **"What is the most important information I should know about TUZISTRA XR?"**
- Take TUZISTRA XR exactly as your healthcare provider tells you to take it. **Do not** change your dose without talking to your healthcare provider.
- Take TUZISTRA XR by mouth only. TUZISTRA XR is usually taken every 12 hours. **Do not** take more than 20 mL of TUZISTRA XR in 24 hours.
- **Do not** mix TUZISTRA XR with other fluids or medicines.
- Take TUZISTRA XR using an accurate milliliter (mL) measuring device. If you do not have one, ask your pharmacist to give you a measuring device to measure the correct amount of TUZISTRA XR. **Do not use a household teaspoon to measure your medicine. You may accidently take too much.**
- **Do not** overfill the measuring device.
- Rinse the measuring device with water after each use.
- If you take too much TUZISTRA XR, call your healthcare provider or go to the nearest hospital emergency room right away.
- Tell your healthcare provider if your cough does not get better within 5 days of treatment with TUZISTRA XR.

What should I avoid doing while taking TUZISTRA XR?

- Avoid driving a car or operating machinery during treatment with TUZISTRA XR. TUZISTRA XR can cause you to be drowsy, slow your thinking and motor skills, and affect your vision.
- **Do not** drink alcohol during treatment with TUZISTRA XR. Drinking alcohol can increase your chances of having serious side effects.

Avoid the use of TUZISTRA XR if you:

- are pregnant. Use of TUZISTRA XR during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Tell your healthcare provider right away if you are pregnant or think you may be pregnant.
- are breastfeeding. Use of TUZISTRA XR while breastfeeding can cause severe breathing problems (respiratory depression) in your breastfed infant that could be life-threatening.

What are the possible side effects of TUZISTRA XR?
TUZISTRA XR can cause serious side effects, including:

- See **"What is the most important information I should know about TUZISTRA XR?"**
- **Bowel problems including severe constipation or stomach pain.** See **"Who should not take TUZISTRA XR?"**
- **Increased pressure in your head (intracranial)**. Avoid the use of TUZISTRA XR if you have a head injury or have been told that you have changes in the tissue of your brain (brain lesions) or increased pressure in your head.
- **Increased risk of seizures in people with seizure disorders**. If you have a seizure disorder, TUZISTRA XR may increase how often you have seizures.
- **Low blood pressure**. A sudden drop in blood pressure can happen in some people during treatment with TUZISTRA XR and this may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). Your risk of having this problem may be increased if you take TUZISTRA XR with certain other medicines that lower blood pressure. If you have any of these symptoms while taking TUZISTRA XR, sit or lie down. Do not change your body position too fast. Get up slowly from sitting or lying down.
- **Adrenal gland problems**. TUZISTRA XR can cause serious and life-threatening adrenal gland problems. Your healthcare provider may do blood tests to check for adrenal gland problems. Call your healthcare provider right away if you have any of these symptoms:
- nausea
- vomiting
- not wanting to eat (anorexia)
- fatigue
- weakness
- dizziness
- low blood pressure

The most common side effects of TUZISTRA XR include:

- sleepiness
- confusion
- coordination problems
- decrease in mental and physical performance
- lack of energy
- lightheadedness
- dizziness
- headache
- dry mouth
- sweating
- nausea
- vomiting
- constipation

These are not all the possible side effects of TUZISTRA XR.
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 at room temperature between 68°F to 77°F (20°C to 25°C).
- Store TUZISTRA XR in a tightly closed container, in a dry, cool place away from heat or direct sunlight.
- **Keep TUZISTRA XR and all medicines out of the reach of children.**

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

General information about the safe and effective use of TUZISTRA XR.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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 symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about TUZISTRA XR that is written for health professionals.

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

for:

Aytu BioScience, Inc.
373 Inverness Parkway, Suite 206
Englewood, CO 80112

For more information call 1-855-AYTU BIO (1-855-298-8246)

LB8553 Rev.00 Revised: October 2018

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 10/2018