HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REZIRA® Oral Solution safely and effectively. See full prescribing information for REZIRA Oral Solution. CII

REZIRA (hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution.
Initial U.S. Approval: 2011

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

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

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

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

----------INDICATIONS AND USAGE----------

REZIRA Oral Solution is a combination product containing an antitussive and nasal decongestant indicated for:

- Relief of cough and nasal congestion associated with common cold.

Important Limitations of Use:
Not indicated for pediatric patients under 18 years of age

----------DOSAGE AND ADMINISTRATION----------

For oral use only.

- Adults 18 years of age and older: 5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

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

----------ADVERSE REACTIONS----------

The most common adverse reactions of REZIRA Oral Solution include: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, nervousness, sleeplessness, tremor, or arrhythmia. (6)

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

----------DRUG INTERACTIONS----------

- Benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants may exhibit additive CNS depression. Avoid using with REZIRA Oral Solution. (7.1)
- MAOIs or tricyclic antidepressants: Do not use. May increase the effect of either the antidepressant or hydrocodone, may cause increase in blood pressure or hypertensive crisis may occur. (7.2)
- Anticholinergic drugs: Use with caution in order to avoid paralytic ileus and excessive anticholinergic effects. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: 1/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full Prescribing Information are not listed.

CII

FULL PRESCRIBING INFORMATION

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

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

1 INDICATIONS AND USAGE

1.1 Common Cold

REZIRA® Oral Solution (hydrocodone bitartrate and pseudoephedrine hydrochloride) is indicated for:

Relief of cough and nasal congestion associated with common cold.

Important Limitations of Use:

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

2 DOSAGE AND ADMINISTRATION

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

2.1 Adults 18 years of age and Older

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

REZIRA Oral Solution is contraindicated in:

- Patients with known hypersensitivity to hydrocodone bitartrate, pseudoephedrine hydrochloride, or any of the inactive ingredients of REZIRA Oral Solution.
- Patients receiving MAOI therapy or within 14 days of stopping such therapy *[see Drug Interactions (7.2)]*.

- Patients with narrow angle glaucoma, urinary retention, severe hypertension or severe coronary artery disease.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacologic properties, it is reasonable to expect similar risk with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol.

Advise both patients and caregivers about the risks of respiratory depression and sedation if REZIRA is used with benzodiazepines, alcohol, or other CNS depressants *[see Patient Counseling Information (17.3)]*.

5.2 Respiratory Depression

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

5.3 Drug Dependence

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

5.4 Head Injury and Increased Intracranial Pressure

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

5.5 Activities Requiring Mental Alertness

Hydrocodone bitartrate, one of the active ingredients in REZIRA Oral Solution, may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Advise patients to avoid engaging in hazardous tasks requiring mental alertness and motor coordination after ingestion of REZIRA Oral Solution. Concurrent use of REZIRA Oral Solution with alcohol or other central nervous system depressants should be avoided because additional impairment of central nervous system performance may occur.

5.6 Acute Abdominal Conditions

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

5.7 Co-administration with Anticholinergics

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

5.8 Co-administration with MAOIs or Tricyclic Antidepressants

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

5.9 Cardiovascular and Central Nervous System Effects

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

5.10 Dosing

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

5.11 Coexisting Conditions

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

5.12 Renal Impairment

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

5.13 Hepatic Impairment

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

6 ADVERSE REACTIONS

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

- Respiratory depression *[see Warnings and Precautions (5.2) and Overdosage (10)]*
- Drug dependence *[see Warnings and Precautions (5.3)]*
- Increased intracranial pressure *[see Warnings and Precautions (543) and Overdosage (10)]*
- Decreased mental alertness with impaired mental and/or physical abilities *[see Warnings and Precautions (5.5)]*
- Paralytic ileus *[see Warnings and Precautions (5.6)]*

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

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

The most common adverse reactions are central nervous system and cardiovascular reactions and include the following: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, nervousness, sleeplessness, tremor or arrhythmia.

Other adverse reactions include:

Gastrointestinal System: Nausea and vomiting (more frequent in ambulatory than in recumbent patients), constipation.

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

Cardiovascular System: Fast, slow heartbeat, hypertension, hypotension, orthostatic hypotension, palpitation, shock-like state, syncope.

Dermatological System: Skin rash, pruritus.

7 DRUG INTERACTIONS

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

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

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

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Anticholinergic Drugs

Hydrocodone should be administered cautiously to persons receiving anticholinergic drugs in order to avoid paralytic ileus and excessive anticholinergic effects *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well controlled studies of REZIRA Oral Solution in pregnant women. Reproductive toxicity studies have not been conducted with REZIRA Oral Solution; however, studies are available with an individual active ingredient or related active ingredient. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. Because animal reproduction studies are not always predictive of human response, REZIRA Oral Solution should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Hydrocodone:

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

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Caution should be exercised when REZIRA is administered to nursing mothers. Hydrocodone and pseudoephedrine are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from REZIRA Oral Solution, a decision should be

made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

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

9.3 Dependence

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

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of

continued oral opioid use, although some mild degree of physical dependence may develop after a few days of opioid therapy.

10 OVERDOSAGE

No human overdosage data are available for REZIRA Oral Solution.

Hydrocodone:

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

Pseudoephedrine:

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

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

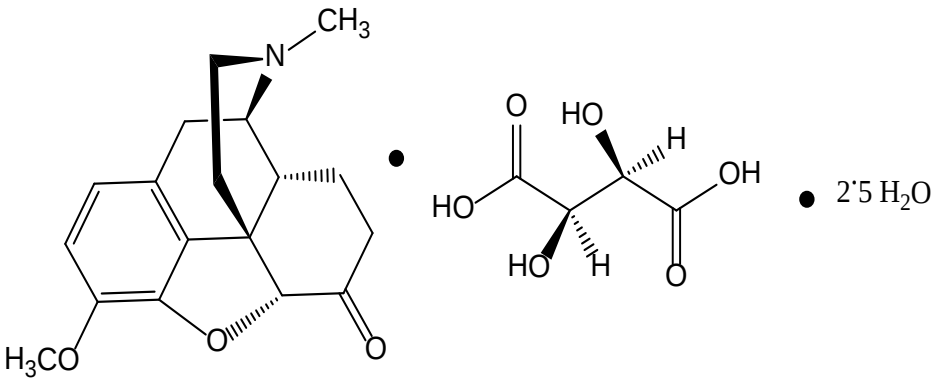
11 DESCRIPTION

REZIRA Oral Solution contains hydrocodone bitartrate (a semisynthetic centrally-acting opioid antitussive) and pseudoephedrine hydrochloride (a sympathomimetic amine).

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

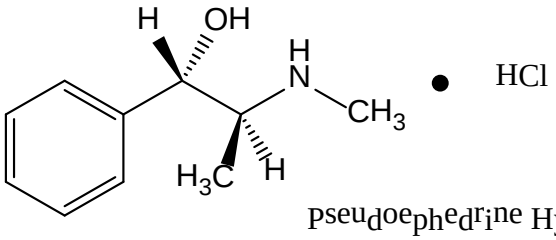
REZIRA Oral Solution also contains: citric acid anhydrous, glycerin, grape flavor, methylparaben, propylene glycol, propylparaben, purified water, sodium citrate, sodium saccharin, and sucrose.

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



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

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.3 Pharmacokinetics

Systemic exposure (in terms of peak plasma concentrations and area under plasma concentration versus time curve) of hydrocodone bitartrate and pseudoephedrine hydrochloride after single-dose administration of 5 mg

hydrocodone and 60 mg pseudoephedrine are equivalent to respective reference solutions of 5 mL hydrocodone bitartrate (5 mg/5 mL) and 5 mL pseudoephedrine hydrochloride (60 mg/5 mL).

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

Specific Populations

Renal Impairment

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Hydrocodone:

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

Pseudoephedrine:

Two-year feeding studies in rats and mice demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 0.3 and 0.5 times, respectively, the MRHDD of pseudoephedrine hydrochloride on a mg/m^2 basis).

14 CLINICAL STUDIES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

White HDPE bottles of one pint (480 mL): NDC 63717-875-16

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

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

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

17.1 Overdosage

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

17.2 Dosing

Patients should be advised to measure REZIRA Oral Solution with an accurate milliliter measuring device. Patients should be informed that a household teaspoon is not an accurate measuring device and could lead to overdosage, especially when half a teaspoon is measured. Patients should be advised to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose *[see Dosing and Administration (2) Warnings and Precautions (5.10)]*.

17.3 Interactions with Benzodiazepines and Other Central Nervous System Depressants

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

17.4 Activities Requiring Mental Alertness

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

17.5 Drug Dependence

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

17.6 MAOIs

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

Manufactured for: Hawthorn Pharmaceuticals, Inc., Morristown, NJ 07960

HI246

Rev 1/2017

MEDICATION GUIDE

REZIRA® (re-zear-uh)

(hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution, CII

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

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

What is REZIRA?

- REZIRA is a prescription medicine used to treat a cough and nasal congestion that you can have with the common cold. REZIRA contains 2 medicines, hydrocodone and pseudoephedrine. Hydrocodone is a narcotic cough suppressant. Pseudoephedrine is a decongestant.
- **REZIRA is a federal controlled substance (C-II) because it contains hydrocodone that can be abused or lead to dependence.** Keep REZIRA in a safe place to prevent misuse and abuse. Selling or giving away REZIRA 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.
- REZIRA is not for children under 18 years of age. It is not known if REZIRA is safe and effective in children.

Who should not take REZIRA?

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

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

- o have a drug dependence
- o have lung or breathing problems
- o have had a head injury
- o have pain in your stomach-area (abdomen)
- o have a history of severe or persistent cough
- o have prostate problems
- o have problems with your urinary tract (urethral stricture)
- o plan to have surgery
- o drink alcohol
- o have kidney or liver problems
- o have diabetes
- o have thyroid problems, such as hypothyroidism
- o have Addison’s disease
- o are pregnant or plan to become pregnant. It is not known if REZIRA will harm your unborn baby. You and your healthcare provider should decide if you should take REZIRA while you are pregnant.

- are breastfeeding or plan to breastfeed. Hydrocodone and pseudoephedrine pass into your breast milk. You and your healthcare provider should decide if you will take REZIRA or breastfeed. You should not do both.

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

Taking REZIRA with certain other medicines can cause side effects or affect how well REZIRA or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

Especially tell your healthcare provider if you:

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

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

How should I take REZIRA?

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

What should I avoid while taking REZIRA?

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

What are the possible side effects of REZIRA?

REZIRA may cause serious side effects, including:

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

The most common side effects of REZIRA include:

- sleepiness
- confusion
- nausea and vomiting
- difficulty urinating
- trouble breathing
- mood changes, including anxiety, fear, nervousness, and feeling low (dysphoria)
- dizziness

These are not all the possible side effects of REZIRA.

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 REZIRA?

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

General information about the safe and effective use of REZIRA.

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

What are the ingredients in REZIRA?

Active ingredients: hydrocodone bitartrate and pseudoephedrine hydrochloride

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

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

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: January 2017