

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**ZERVIAE™ (cetirizine ophthalmic solution) 0.24%, for topical ophthalmic use**

**Initial U.S. Approval: 1995**

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

ZERVIAE (cetirizine ophthalmic solution) 0.24% is a histamine-1 (H1) receptor antagonist indicated for treatment of ocular itching associated with allergic conjunctivitis. (1)

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

The recommended dose is one drop in each affected eye twice daily. (2)

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

Ophthalmic solution: 2.4 mg cetirizine in 1 mL sterile solution (0.24%). (3)

-----**CONTRAINDICATIONS**-----

None. (4)

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

Contamination of Tip and Solution. To prevent contaminating the dropper tip and solution, advise patients not to touch the eyelids or surrounding areas with the dropper tip of the bottle. (5.1)

-----**ADVERSE REACTIONS**-----

The most common adverse reactions (1–7%) were ocular hyperemia, instillation site pain, and visual acuity reduced. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Nicox Ophthalmics, Inc. at 1-XXX-XXX-XXXX or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2017

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

5.1 Contamination of Tip and Solution

5.2 Contact Lens Wear

**6 ADVERSE REACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

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

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

ZERVIAE™ (cetirizine ophthalmic solution) 0.24% is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

### **2 DOSAGE AND ADMINISTRATION**

The recommended dosage of ZERVIAE is to instill one drop in each affected eye twice daily (approximately 8 hours apart).

### **3 DOSAGE FORMS AND STRENGTHS**

Cetirizine ophthalmic solution, 0.24% is a sterile, buffered, clear, colorless aqueous solution containing cetirizine 0.24% (equivalent to cetirizine hydrochloride 0.29%).

### **4 CONTRAINDICATIONS**

None.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Contamination of Tip and Solution**

As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle to prevent contaminating the tip and solution. Keep the bottle closed when not in use.

#### **5.2 Contact Lens Wear**

Patients should be advised not to wear a contact lens if their eye is red.

ZERVIAE should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of ZERVIAE. The preservative in ZERVIAE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of ZERVIAE.

### **6 ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates in practice.

In seven clinical trials, patients with allergic conjunctivitis or those at a risk of developing allergic conjunctivitis received one drop of either cetirizine (N=511) or vehicle (N=329) in one or both eyes. The most commonly reported adverse reactions occurred in approximately 1–7% of patients treated with either ZERVIAE or vehicle. These reactions were ocular hyperemia, instillation site pain, and visual acuity reduced.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Risk Summary*

There were no adequate or well-controlled studies with ZERVIAE™ (cetirizine ophthalmic solution) 0.24% in pregnant women. Cetirizine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### *Data*

##### Animal Data

Cetirizine was not teratogenic in mice, rats, or rabbits at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 1300, 4930, and 7400 times the maximum recommended human ophthalmic dose (MRHOD), on a mg/m<sup>2</sup> basis).

### 8.2 Lactation

#### *Risk Summary*

Cetirizine has been reported to be excreted in human breast milk following oral administration. Multiple doses of oral dose cetirizine (10 mg tablets once daily for 10 days) resulted in systemic levels (Mean C<sub>max</sub> = 311 ng/mL) that were 100 times higher than the observed human exposure (Mean C<sub>max</sub> = 3.1 ng/mL) following twice-daily administration of cetirizine ophthalmic solution 0.24% to both eyes for one week [see *Clinical Pharmacology 12.3*]. Comparable bioavailability has been found between the tablet and syrup dosage forms. However, it is not known whether the systemic absorption resulting from topical ocular administration of ZERVIAE could produce detectable quantities in human breast milk.

There is no adequate information regarding the effects of cetirizine on breastfed infants, or the effects on milk production to inform risk of ZERVIAE to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZERVIAE and any potential adverse effects on the breastfed child from ZERVIAE.

### 8.4 Pediatric Use

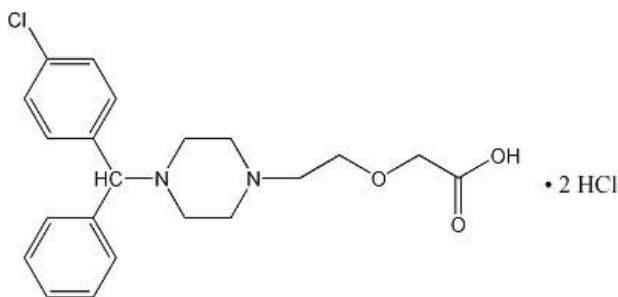
The safety and effectiveness of ZERVIAE has been established in pediatric patients two years of age and older. Use of ZERVIAE in these pediatric patients is supported by evidence from adequate and well-controlled studies of ZERVIAE in pediatric and adult patients.

### 8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

## 11 DESCRIPTION

ZERVIAE is a sterile ophthalmic solution containing cetirizine, which is a histamine-1 (H<sub>1</sub>) receptor antagonist, for topical administration to the eyes. Cetirizine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 461.8 and a molecular formula of C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>•2HCl. The chemical structure is presented below:



Chemical Name: (RS)-2-[2-[4-[(4-Chlorophenyl) phenylmethyl] piperazin-1-yl] ethoxy] acetic acid, dihydrochloride

Each mL of ZERVIAE contains an active ingredient [cetirizine 2.40 mg (equivalent to 2.85 mg of cetirizine hydrochloride)] and the following inactive ingredients: benzalkonium chloride 0.010% (preservative); glycerin; sodium phosphate, dibasic; edetate disodium; polyethylene glycol 400; polysorbate 80; hypromellose; hydrochloric acid/sodium hydroxide (to adjust pH); and water for injection. ZERVIAE solution has a pH of approximately 7.0 and osmolality of approximately 300 mOsm/kg.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

ZERVIAE, an antihistamine, is a histamine-1 (H<sub>1</sub>) receptor antagonist. Its effects are mediated via selective inhibition of H<sub>1</sub> histamine receptors. The antihistaminic activity of cetirizine has been documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. *In vitro* receptor binding studies have shown no measurable affinity for other than H<sub>1</sub> receptors.

### 12.3 Pharmacokinetics

In healthy subjects, bilateral topical ocular dosing of one drop of ZERVIAE™ (cetirizine ophthalmic solution) 0.24% resulted in a mean cetirizine plasma C<sub>max</sub> of 1.7 ng/mL following a single dose and 3.1 ng/mL after twice-daily dosing for one week. The observed mean terminal half-life of cetirizine was 8.6 hours following a single dose and 8.2 hours after twice-daily dosing of ZERVIAE for one week.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### *Carcinogenicity*

In a 2-year carcinogenicity study in rats, orally administered cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 550 times the MRHOD, on a mg/m<sup>2</sup> basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 220 times the MRHOD, on a mg/m<sup>2</sup> basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 55 times the MRHOD, on a mg/m<sup>2</sup> basis). The clinical significance of these findings during long-term use of cetirizine is not known.

#### *Mutagenesis*

Cetirizine was not mutagenic in the Ames test or in an *in vivo* micronucleus test in rats. Cetirizine was not clastogenic in the human lymphocyte assay or the mouse lymphoma assay.

### Impairment of Fertility

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 875 times the MRHOD on a mg/m<sup>2</sup> basis).

## 14 CLINICAL STUDIES

The efficacy of ZERVIAE was established in three randomized, double-masked, placebo-controlled, conjunctival allergen challenge (CAC) clinical trials in patients with a history of allergic conjunctivitis. Onset and duration of action were evaluated in two of these trials in which patients were randomized to receive ZERVIAE or vehicle ophthalmic solutions. Patients were evaluated with an ocular itching severity score ranging from 0 (no itching) to 4 (incapacitating itch) at several time points after CAC administration. Table 1 displays data from the mean ocular itching severity scores after ocular administration of an antigen using the CAC model. A one unit difference compared to vehicle is considered a clinically meaningful change in the ocular itching severity score.

Patients treated with ZERVIAE demonstrated statistically and clinically significantly less ocular itching compared to vehicle at 15 minutes and 8 hours after treatment.

**Table 1 Itching Scores in the ITT Population by Treatment Group and Treatment Difference**

Statistics	Study 1				Study 2			
	15 minutes post-treatment		8 hours post-treatment		15 minutes post-treatment		8 hours post-treatment	
	ZERVIAE N=50	Vehicle N=50	ZERVIAE N=50	Vehicle N=50	ZERVIAE N=51	Vehicle N=50	ZERVIAE N=51	Vehicle N=50
<b>3 Minute Post-CAC</b>								
Mean	1.00	2.38	1.76	2.69	1.01	2.54	1.94	2.86
Treatment Difference (95% CI) <sup>1</sup>	-1.38 (-1.72, -1.05)*		-0.93 (-1.26, -0.61)*		-1.53 (-1.92, -1.15)*		-0.92 (-1.25, -0.58)*	
<b>5 Minute Post-CAC</b>								
Mean	1.18	2.43	1.85	2.74	1.17	2.51	2.03	1.82
Treatment Difference (95% CI) <sup>1</sup>	-1.25 (-1.58, -0.91)*		-0.89 (-1.24, -0.54)*		-1.34 (-1.71, -0.97)*		-0.90 (-1.23, -0.57)*	
<b>7 Minute Post-CAC</b>								
Mean	1.11	2.11	1.54	2.53	1.15	2.23	2.94	2.66
Treatment Difference (95% CI) <sup>1</sup>	-1.00 (-1.35, -0.65)*		-0.99 (-1.40, -0.59)*		-1.07 (-1.46, -0.69)*		-0.84 (-1.21, -0.48)*	

<sup>1</sup> Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point.  
\* p<0.05

## 16 HOW SUPPLIED/STORAGE AND HANDLING

ZERVIAE is a sterile, buffered, clear, colorless aqueous solution containing cetirizine 0.24% (equivalent to cetirizine hydrochloride 0.29%) supplied in a white low-density polyethylene multi-dose ophthalmic bottle with a low-density polyethylene dropper tip and a white polypropylene cap. ZERVIAE is supplied in a 7.5 mL bottle that contains 5 mL and 10 mL bottle that contains 7.5 mL cetirizine ophthalmic solution, 2.40 mg [equivalent to 2.85 mg cetirizine hydrochloride in one mL solution].

5 mL fill in a 7.5 mL bottle NDC XXXXX-XXXX-5  
7.5 mL fill in a 10 mL bottle NDC XXXXX-XXXX-7

**Storage:** Store at 15°C to 25°C (59°F to 77°F).

## 17 PATIENT COUNSELING INFORMATION

- Risk of Contamination: Advise patients not to touch dropper tip to eyelids or surrounding areas, as this may contaminate the dropper tip and ophthalmic solution. Advise patients to keep the bottle closed when not in use.
- Concomitant Use of Contact Lenses: Advise patients not to wear contact lenses if their eyes are red. Advise patients that ZERVIAE should not be used to treat contact lens-related irritation. Advise patients to remove contact lenses prior to instillation of ZERVIAE. The preservative in ZERVIAE solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted ten minutes following administration of ZERVIAE.

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Manufactured by: Akorn, Inc.  
Lake Forest, IL 60045

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