ZERVIATE- cetirizine solution/ drops
Eyevance Pharmaceuticals

HIGHLIGHTS OF PRESCRIBING INFORMATION
ZERVIATE™ (cetirizine ophthalmic solution) 0.24%, for topical ophthalmic use

These highlights do not include all the information needed to use ZERVIATE safely and effectively. See full prescribing information for ZERVIATE.Initial U.S. Approval: 1995

RECENT MAJOR CHANGES

Dosage and Administration (2)	2/2020
Warnings and Precautions (5.1)	2/2020

INDICATIONS AND USAGE

ZERVIATE (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

Sterile ophthalmic solution: 2.4 mg cetirizine in 1 mL 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 Eyevance Pharmaceuticals, LLC at 1-844-750-1159 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZERVIATE™ (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 ZERVIATE is to instill one drop in each affected eye twice daily (approximately 8 hours apart).

The single-use containers are to be used immediately after opening and can be used to dose both eyes. Discard the single-use container and any remaining contents after administration. The single-use containers should be stored in the original foil pouch until ready to use.

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 or tip of the single-use container in order to avoid injury to the eye and to prevent contaminating the tip and solution. Keep the multi-dose bottle closed when not in use. Discard the single-use container after using in each eye.

5.2 Contact Lens Wear

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

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

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 ZERVIATE 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 ZERVIATE™ (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.

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^2 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_{max} = 311 ng/mL) that were 100 times higher than the observed human exposure (Mean C_{max} = 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 ZERVIATE 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 ZERVIATE to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZERVIATE and any potential adverse effects on the breastfed child from ZERVIATE.

8.4 Pediatric Use

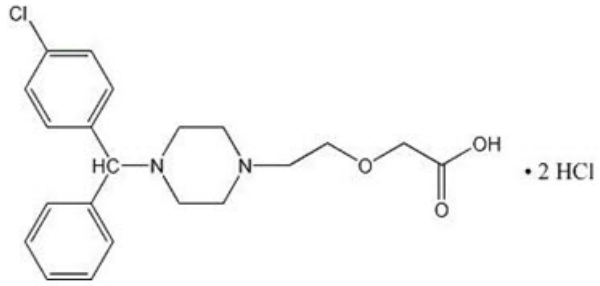
The safety and effectiveness of ZERVIATE has been established in pediatric patients two years of age and older. Use of ZERVIATE in these pediatric patients is supported by evidence from adequate and well-controlled studies of ZERVIATE in pediatric and adult patients.

8.5 Geriatric Use

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

11 DESCRIPTION

ZERVIATE is a sterile opthalmic solution containing cetirizene, which is a histamine-1 (H1) 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 C21H25CIN203•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 ZERVIATE 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. ZERVIATE solution has a pH of approximately 7.0 and osmolality of approximately 300 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZERVIATE is a histamine-1 (H1) receptor antagonist (antihistamine) and an inhibitor of release of histamine from mast cells. Its effects are mediated via selective inhibition of H_1 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 H1 receptors.

12.3 Pharmacokinetics

In healthy subjects, bilateral topical ocular dosing of one drop of ZERVIATE™ (cetirizine ophthalmic solution) 0.24% resulted in a mean cetirizine plasma C_{max} 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 ZERVIATE 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^2 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^2 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^2 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^2 basis).

14 CLINICAL STUDIES

The efficacy of ZERVIATE 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 ZERVIATE 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 ZERVIATE 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	
	ZERVIATE N=50	Vehicle N=50	ZERVIATE N=50	Vehicle N=50	ZERVIATE N=51	Vehicle N=50	ZERVIATE N=51	Vehicle N=50
3 Minute Post-CAC								
Mean	1.00	2.38	1.76	2.69	1.01	2.54	1.94	2.86
Treatment Difference (95% CI) [1]	-1.38 (-1.72, -1.05)*		-0.93 (-1.26, -0.61)*		-1.53 (-1.92, -1.15)*		-0.92 (-1.25, -0.58)*	
5 Minute Post-CAC								
Mean	1.18	2.43	1.85	2.74	1.17	2.51	2.03	1.82
Treatment Difference (95% CI) [1]	-1.25 (-1.58, -0.91)*		-0.89 (-1.24, -0.54)*		-1.34 (-1.71, -0.97)*		-0.90 (-1.23, -0.57)*	
7 Minute Post-CAC								
Mean	1.11	2.11	1.54	2.53	1.15	2.23	2.94	2.66
Treatment Difference (95% CI) [1]	-1.00 (-1.35, -0.65)*		-0.99 (-1.40, -0.59)*		-1.07 (-1.46, -0.69)*		-0.84 (-1.21, -0.48)*	

[1] 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

ZERVIATE 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. ZERVIATE 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]. ZERVIATE is also supplied in 5 low-density polyethylene 0.2 mL single-use containers within a foil pouch.

5 mL fill in a 7.5 mL bottle	NDC 71776-024-05
7.5 mL fill in a 10 mL bottle	NDC 71776-024-08
Carton of 30 single-use containers	NDC 71776-024-30

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 ZERVIATE should not be used to treat contact lens-related irritation. Advise patients to remove contact lenses prior to instillation of ZERVIATE. The preservative in ZERVIATE solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted ten minutes following administration of ZERVIATE.

ZPI0000 Rev 2/2020

Distributed by:
Eyevance Pharmaceuticals, LLC.

Fort Worth, TX 76102

U.S. Patents: 8,829,005; 9,254,286; 9,750,684; 9,993,471

eyevance

ZERVIATE™

cetirizine ophthalmic solution, 0.24%

NDC 71776-024-30

This unit not intended for individual sale

ZERVIATE™

cetirizine ophthalmic solution, 0.24%

Each mL contains:
Active: 2.4 mg of cetirizine (equivalent to 2.85 mg cetirizine hydrochloride)
STORAGE: Store at 15°-25°C (59°-77°F) Store single-use vials in original foil pouch, protected from light
FOR TOPICAL OPHTHALMIC USE
Manufactured by: Excelvision, 07100 Annonay, France

5 Single-Use Vials (0.2 mL each)

eyevance pharmaceuticals

Sterile

Rx Only

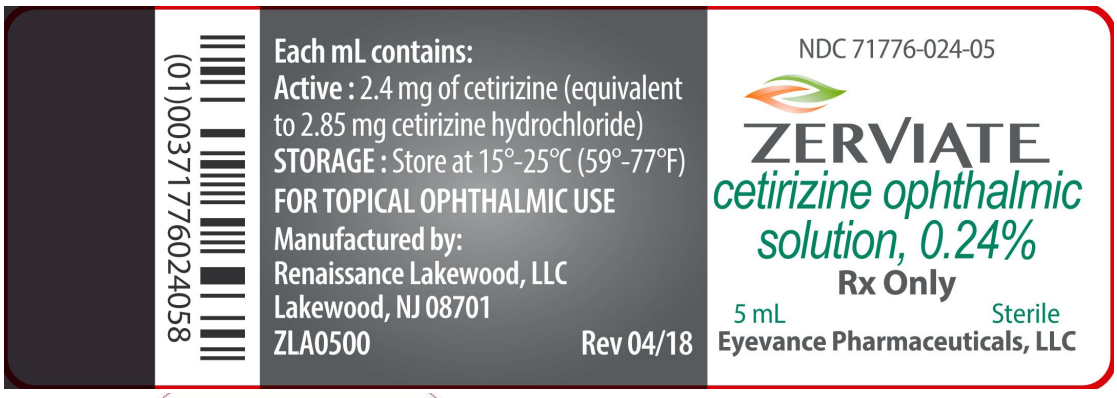
ZTOW0100 Rev 09/19

24104100

LOT

EXP


NDC 71776-024-05
ZERVIATE
cetirizine ophthalmic solution, 0.24%
Rx Only
FOR TOPICAL OPHTHALMIC USE
5 mL
Sterile
Eyevance Pharmaceuticals, LLC
X3178602
Each mL contains:
Active : 2.4 mg of cetirizine (equivalent to 2.85 mg cetirizine hydrochloride)
Inactives: Benzalkonium chloride (0.01%); edetate disodium; glycerin; hypromellose; polyethylene glycol 400; polysorbate 80; sodium phosphate, dibasic; hydrochloric acid and/or sodium hydroxide may be added (to adjust pH) and water for injection
Manufactured by:
Renaissance Lakewood, LLC
Lakewood, NJ 08701
Country of Origin: Italy
ZCA0500
Rev 04/18
ZCA0500
ZERVIATE
cetirizine ophthalmic solution, 0.24%
NDC 71776-024-05
ZERVIATE
cetirizine ophthalmic solution, 0.24%
Rx Only
FOR TOPICAL OPHTHALMIC USE
5 mL
Sterile
Eyevance Pharmaceuticals, LLC
Usual Dosage: Instill one drop in the affected eye twice daily.
STORAGE: Store at 15°-25°C (59°-77°F)
371776024058



ZERVIATE

cetirizine solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:71776-024
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CETIRIZINE (UNII: YO7261ME24) (CETIRIZINE - UNII:YO7261ME24)	CETIRIZINE	2.4 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
GLYCERIN (UNII: PDC6A3C0OX)	
HYPROMELLOSE 2910 (4000 MPA.S) (UNII: RN3152OP35)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SODIUM PHOSPHATE, DIBASIC (UNII: GR686LBA74)	

HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71776-024-05	1 in 1 CARTON	02/19/2019	
1		5 mL in 1 BOTTLE, DROPPER; Type 0: Not a Combination Product		
2	NDC:71776-024-01	5 in 1 CARTON	07/07/2019	
2		0.2 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		
3	NDC:71776-024-30	30 in 1 CARTON	02/10/2020	
3		0.2 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208694	02/19/2019	

Labeler - Eyevance Pharmaceuticals (080876046)

Registrant - Eyevance Pharmaceuticals (080876046)

Establishment

Name	Address	ID/FEI	Business Operations
Renaissance Lakewood LLC		077744035	manufacture(71776-024) , analysis(71776-024) , pack(71776-024) , label(71776-024)

Establishment

Name	Address	ID/FEI	Business Operations
Excelvision		274234566	manufacture(71776-024) , analysis(71776-024) , label(71776-024) , pack(71776-024)

Establishment

Name	Address	ID/FEI	Business Operations
COSMA Spa		428655732	api manufacture(71776-024)

Revised: 2/2020 Eyevance Pharmaceuticals