Medical Officer's Review of NDA 208694
Resubmission

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| **NDA** 208694 | **Submission Date:** March 8, 2017 |
| Resubmission | **Received Date:** March 8, 2017 |
| SDN-017 | **Review Date:** April 24, 2017 |
| **Applicant:** | Nicox Ophthalmics, Inc.<br>777 Main St., Suite 1292<br>Fort Worth, TX 76102<br>Contact: Michael Bergamini<br>(817) 798-8588 |
| **Drug:** | Zerviate (cetirizine ophthalmic solution) 0.24% |
| **Pharmacologic Category:** | Histamine $H_1$ receptor antagonist |
| **Dosage Form and Route of Administration:** | Topical ophthalmic solution |

**Submitted:**

Submitted is a resubmission of NDA 20869, Zerviate (cetirizine ophthalmic solution) 0.24%. The original NDA was submitted on April 18, 2016. A Complete Response (CR) letter dated October 7, 2016 was issued. Applicant now believes that the deficiency identified in the CR regarding the good manufacturing practice (GMP) status of the drug substance manufacturer has been rectified. Included in this submission is a resubmission of a proprietary name review and a safety update.

**Reviewer's Comments:**

*No new information was identified in the safety update. From a clinical perspective, our conclusion on the safety and efficacy of cetirizine 0.24% dosed twice daily for the treatment of ocular itching associated with allergic conjunctivitis is unchanged. See original Clinical review dated 9/26/16 in DARRTS.*

*Attached is the Agency's recommended labeling.*

**Conclusion/Recommended Regulatory Action:**

NDA 208694 is recommended for approval with the labeling identified in this review.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 208694
DTOP/Div/Files
DTOP/CSO/Germain
DTOP/MO/Lim
DTOP/CTL/Boyd
DTOP/Dep Div Director/Chambers

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use ZERVIATE safely and effectively. See full prescribing information for ZERVIATE.**

**ZERVIATE™ (cetirizine ophthalmic solution) 0.24%, for topical ophthalmic use**
**Initial U.S. Approval: 1995**

**----------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----------**
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.***

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 05/2017**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



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

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**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).

## 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.

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

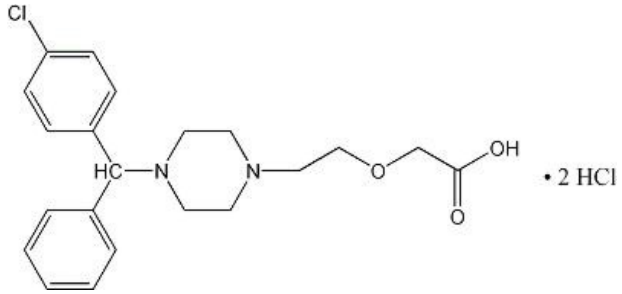
The safety and effectiveness of ZERVIATE has been established in pediatric patients two years of age and older. Use of ZERVIATE in these pediatric patients is supported by evidence from adequate and well-controlled studies of ZERVIATE in pediatric and adult patients.

### 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 ophthalmic solution containing cetirizine, 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 $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$. 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, an antihistamine, is a histamine-1 (H1) receptor antagonist. 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**

| | Study 1 | | | | Study 2 | | | |
|---|---|---|---|---|---|---|---|---|
| Statistics | 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].

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 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.

XXX 2017
Manufactured by: Akorn, Inc.
Lake Forest, IL 60045

U.S. Patents: 8,829,005; 9,254,286

**7.5 mL Carton**


Move FOR TOPICAL OPHTHALMIC USE to principle display panel.

The established name should be revised on the carton labels to a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

Please ensure the box marked "UPC Code" is a barcode referring to the product's NDC number.

(b) (4)

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Move FOR TOPICAL OPHTHALMIC USE to principle display panel.

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Please ensure the box marked "UPC Code" is a barcode referring to the product's NDC number.

**7.5 mL container label**


Please ensure the box marked "UPC Code" is a barcode referring to the product's NDC number.



Please ensure the box marked "UPC Code" is a barcode referring to the product's NDC number.

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/s/

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LUCIOUS LIM
05/16/2017

WILLIAM M BOYD
05/16/2017