Office of Clinical Pharmacology Review

NDA or BLA Number	208694
Link to EDR	EDR Link
Submission Date	April 18,2016
Submission Type	Standard
Brand Name	Zerviate
Generic Name	Cetirizine ophthalmic solution
Dosage Form and Strength	0.24% cetirizine ophthalmic solution
Route of Administration	Topical: ocular
Proposed Indication	Treatment of ocular itching associated with allergic conjunctivitis
Proposed Dosing Regimen	Instill one drop in each affected eye twice daily
Applicant	Nicox Ophthalmics Inc
Associated IND	(b) (4), 108558
OCP Review Team	Abhay Joshi, PhD
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1. EXECUTIVE SUMMARY

This NDA 208694 is for Zerviate, which is an ophthalmic solution that contains 0.24% cetirizine hydrochloride. The Applicant is seeking approval for the treatment of ocular itching associated with allergic conjunctivitis. The proposed dosing regimen is to instill one drop (approximately (b) (4) cetirizine/drop) in each affected eye twice daily (BID). In this review, cetirizine hydrochloride is denoted as cetirizine.

Cetirizine is a histamine H1 receptor antagonist, which is approved as Zyrtec® by the FDA in tablet (e.g. as well as in syrup forms, and the maximum approved daily oral dose is 10 mg. Currently, the nonprescription use of cetirizine tablet is approved by the FDA for the following indications in adults and children 6 years of age and older:

- the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat
- the relief of itching due to hives (urticaria)

This NDA is supported by seven clinical studies that evaluated several formulations of cetirizine ophthalmic solution of varying strengths ranging from 0.05% to 0.24%. A final ophthalmic solution formulation at a concentration of 0.24% cetirizine was selected because of its favorable balance of efficacy and comfort. Five studies (3 safety and efficacy, 1 pharmacokinetic (Study 14-100-0007), and 1 safety) were conducted using the final proposed to-be-marketed 0.24% formulation.

One pharmacokinetic study was conducted to assess the systemic exposure resulting from the repeated administration of 0.24% cetirizine ophthalmic solution. Even though the intended site of action for the proposed drug product is the eye and the extent of systemic exposure to cetirizine is not expected to relate directly with efficacy, the results from the abovementioned PK study was utilized to help evaluate safety.

1.1 Recommendations

The Clinical Pharmacology information provided by the Applicant in this submission is acceptable, and the Clinical Pharmacology review team recommends that NDA 208694 for Zerviate (0.24% cetirizine ophthalmic solution) be approved for the treatment of ocular itching associated with allergic conjunctivitis. The Clinical Pharmacology recommendation is based on the results from Study 14-100-0007.

The Reviewer's proposed labeling changes/recommendations in **Section 2.3** will be forwarded to the Applicant.

	Review Issues	Review Issues Recommendations and Comments
1	Assessment of systemic exposure following the proposed clinical dosing regimen	Systemic concentrations of cetirizine were detected in all subjects throughout the 24-hour period following single and multiple dosing. After multiple doses of 0.24% cetirizine ophthalmic solution, the mean peak plasma concentration (C_{max}) of cetirizine was approximately 1.8 times higher than after a single dose. The cetirizine levels resulting from multiple doses of 0.24% cetirizine ophthalmic solution, i.e., one drop in each eye BID for a week, were approximately 100 times lower than the reported mean C_{max} after multiple oral doses of cetirizine, i.e., 10 mg Zyrtec tablet QD for 10 days.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Under the clinical development program, the Applicant has conducted seven clinical studies, which evaluated several different formulations of cetirizine ophthalmic solution at concentrations ranging from 0.05% – 0.24% (Table 1).

Table 1: List of Clinical Studies Conducted with Cetirizine Ophthalmic Solutions (Modified from Table 5.2-1 Listing of All Clinical Studies)

Type of Study	Study ID	Dosage Regimen	Test Product(s); Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety	11-100-0004	QD	Cetirizine 0.05% = 25 0.10% = 26 0.24% = 25 Vehicle = 25	History of allergic conjunctivitis	6 weeks
Efficacy and Safety	11-100-0012	Day 0 and Day 14	Cetirizine 0.24% = 46 Vehicle = 45	Positive history of ocular allergies	Approx. 5 weeks
Safety and Comfort	11-100-0013	Single dose	Formulation 1: Cetirizine 0.17% = 16 0.24% = 15 Formulation 2: Cetirizine 0.24% = 15 Pataday™ = 14	BCVA of 0.7 logMAR or better in each eye	1 day
Efficacy and Safety	12-100-0006	Day 0 and Day 14	Cetirizine 0.24% = 50 Vehicle = 50	Positive history of ocular allergy	Approx. 5weeks
Efficacy and Safety	13-100-0002	Day 0 and Day 14	Cetirizine 0.24% = 51 Vehicle = 50	Positive history of ocular allergy	Approx. 5 weeks
Safety	14-100-0006	BID	Cetirizine 0.24% = 341 Vehicle = 171	Healthy adult and pediatric subjects ≥2 years of age with a history or family history of atopic disease (including allergic conjunctivitis)	Approx. 6 weeks
PK and Safety	14-100-0007	BID	Cetirizine 0.24% = 11	Healthy adult	screening + 1 week bid dosing

From the seven clinical studies listed in Table 1, five studies were conducted with the final proposed to-be-marketed formulation of 0.24% cetirizine ophthalmic solution. From those studies, Study 14-100-0007 had planned PK assessments. The aim of this study was to characterize the PK and safety of the final proposed to-be-marketed formulation: 0.24% cetirizine ophthalmic solution. The study was conducted in healthy adult subjects and PK was assessed following both single dose and multiple doses, i.e., BID for 7 days. Systemic levels of cetirizine were detected in all subjects throughout the 24-hour period following single and multiple dosing. After multiple doses of 0.24% cetirizine ophthalmic solution, the mean C_{max} of cetirizine was approximately 1.8 times higher than the reported mean C_{max} after a single dose. However, the mean C_{max} of cetirizine after multiple doses of 0.24% cetirizine ophthalmic solution, i.e., one drop in each eye BID for a week, were approximately 100 times lower than the mean C_{max} following multiple oral doses of Zyrtec tablets, i.e., 10 mg QD for 10 days, as per the approved Zyrtec labeling.

2.1 Pharmacology and Clinical Pharmacokinetics

The following are the relevant Clinical Pharmacology findings from Study 14-100-0007 that was conducted in support of the proposed drug product. Detailed Clinical Pharmacology information on cetirizine is summarized in Section 3.1.

The objective of Study 14-100-0007 was to characterize the plasma pharmacokinetics and safety profile of 0.24% cetirizine ophthalmic solution following a single dose (one drop/eye) and following one week of BID dosing in healthy adult subjects. Blood samples were collected after both the treatments, i.e., a single bilateral doses and one week of BID bilateral doses. Cetirizine concentrations in human plasma were determined by a reverse-phase chromatography LC-MS/MS method that was validated over a range of 0.1 – 100 ng/mL. Following single and multiple doses of 0.24% cetirizine ophthalmic solution, plasma levels of cetirizine were detected in all dosed subjects. After single bilateral doses of 0.24% cetirizine ophthalmic solution, the mean C_{max} of cetirizine was 1.7 ng/mL and the mean time to maximum concentration was 2.2 hours. After multiple bilateral doses, i.e., BID for a week, the mean C_{max} of cetirizine was 3.1 ng/mL and the mean time to maximum concentration was 1.6 hours. The terminal half-life of cetirizine was 8.6 hours after a single dose and 8.2 hours after multiple doses. After multiple bilateral doses, C_{max} was approximately 1.8 times higher than that observed following single bilateral doses.

The mean C_{max} reported in this study following ocular administration of one drop of 0.24% cetirizine ophthalmic solution BID for one week (i.e., 3.1 ng/mL), was approximately 100 times lower than that observed following multiple oral doses of Zyrtec tablets 10 mg QD for 10 days, i.e., 10 mg tablets QD for 10 days (Source: Zyrtec package insert).

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The proposed dosing is to instill one drop in each affected eye twice daily.

2.2.2 Therapeutic Individualization

Therapeutic individualization is not needed for the proposed 0.24% cetirizine ophthalmic solution for the treatment of ocular itching associated with allergic conjunctivitis.

2.3 Summary of Labeling Recommendations

The Clinical Pharmacology review team has the following labeling recommendations; edits marked in *Red* and strikethrough:

Section 8.2, Lactation*:*

> ***Cetirizine has been reported to be excreted in human breast milk following oral administration. In humans, ~~Multiple~~ multiple oral doses of ~~oral dose~~ cetirizine tablets ~~(10 mg tablets once daily for 10 days)~~ 10 mg once daily for 10 days resulted in peak ~~systemic levels~~ plasma drug concentrations (Mean Cmax = 311 ng/mL) that were ~~ten~~ 100 times higher than ~~the~~ those observed ~~human exposure (Mean Cmax = 3.1 ng/mL)~~ following twice-daily administration of cetirizine ophthalmic solution 0.24% to both eyes for one week (Mean Cmax = 3.1 ng/mL) [see section 12.3]. However, ~~I~~it is not known whether the systemic absorption resulting from topical***

ocular administration of Zerviate could ~~result in sufficient systemic absorption~~ produce detectable quantities in human breast milk. (b) (4) .

Section 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 Cmax of 1.7 ng/mL following a single dose and 3.1 ng/mL after twice-daily dosing for one week. The mean terminal half-life of ~~ZERVIATE~~ cetirizine was 8.6 hours following a single dose and 8.2 hours after twice-daily dosing of Zerviate for one week. ~~short; after a single dose it was 8.6 hours and after multiple doses it was 8.2 hours.~~

3. CLINICAL PHARMACOLOGY REVIEW

Given the approved oral doses of cetirizine are substantially higher than the dose that is being proposed for topical ocular delivery in this NDA, limited Clinical Pharmacology evaluation of the systemic exposure to cetirizine was conducted under the clinical development program for the 0.24% ophthalmic solution. Specifically, the Applicant conducted one pharmacokinetic (PK) study to assess the systemic exposure to cetirizine following one week of BID dosing; for additional details, see Section 4.2 below for PK Study 14-100-0007.

3.1 Clinical Pharmacology Questions

3.1.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

No, the provided Clinical Pharmacology information does not provide supportive evidence of effectiveness. For the proposed ophthalmic product, the intended site of action for cetirizine is the eye; therefore, the extent of systemic exposure does not relate with the proposed drug product's efficacy.

3.1.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen is to instill one drop BID (approximately (b) (4) cetirizine/drop) in each affected eye and this proposed general dosing regimen is appropriate for the general patient population for which the indication is being sought.

4. APPENDICES

4.1 Bioanalytical Method Report

In support of Study 14-100-0007 that included PK assessments, the Applicant has provided a bioanalytical method validation report ARCT2. A reverse-phase chromatography LC-MS/MS method was validated to quantify cetirizine with a dynamic range of 0.1 – 100 ng/mL. Validation parameters are summarized in Table 1.

Table 1: Bioanalytical Methods Validation Report: Summary

[redacted] (b) (4) ***Submitted in Support of the Study 14-100-0007***	
Analyte	Cetirizine
Matrix	Plasma
Analytical Procedure	LC-MS/MS
Sample Preparation	Solid Phase extraction
Validation Range	0.1 – 100 ng/mL (LLOQ = 0.1 ng/mL)
QCs	0.1 ng/mL, 1.3 ng/mL,30 ng/mL,75 ng/mL
Intra-Assay Accuracy (%DEV)	4.11% to 1.39% (-5.30% for LLOQ) (N=6 Run)
Intra-Assay Precision (%CV)	≤ 2.71% (6.04% for LLOQ)
Inter-Assay Accuracy (%DEV)	5.71% to 2.56% (-1.26% for LLOQ) (N=3 Run)
Inter-Assay Precision (%CV)	≤ 6.03% (11.3% for LLOQ)
Long-term stability	84 days at -70°C (±10°C)
Benchtop Stability	>24 hours
Investigative Site	Andover Eye Associates 138 Haverhill Street Andover, MA 01810
Contract Research Organization (CRO)	[redacted] (b) (4)
Analytical Site	
Sample collection	26 Jul 2014 – 10 Aug 2014
Sample receipt	12 Aug 2014
Sample analysis	13 Aug 2014 – 18 Aug 2014
Within the Stability range	Yes

Reviewer's assessment:

Based on the reported validation parameters, the bio-analytical method that was used to quantify cetirizine appears adequate except for the following information on stability data (page 18) of the bio-analytical method validation report [redacted] (b) (4) *:*

> ***"The re-analysis met acceptance criteria suggesting that the analyte is stable and that a slight bias in calibration curve in the original analysis (Run 31375_002) was the cause of the original failure."***

It appears that Run 31375_002, which was reported to have a slight bias, was also used in the following evaluations on 14 May 2014:

- *Matrix effects-Matrix Factor Evaluation*
- *Extraction Efficiency*
- *Short-term Matrix Stability (Benchtopstability) (room temperature)*
- *Room Temperature Extract Stability (Analysis)*
- *Refrigerator Extract Stability (Analysis)*

In Reviewer's opinion, this finding does not appear to be of a significant concern because of the following supportive information:

- *Most samples from the abovementioned evaluations were also analyzed with the other calibration run at later dates, except for the samples form Short-term Matrix Stability evaluation at room temperature*
- *The data from a different Stability Evaluation (10 Jun 2014) provides the supportive evidence that suggest that the cetirizine is stable for 29 hours in human plasma which can be utilized in lieu of Short-Term Matrix Stability data*

Therefore, based on the entirety of information provided by the Applicant, the bio-analytical method that was used to quantify cetirizine is acceptable.

4.2 Individual Study Review

4.2.1 Study 14-100-0007

Title:
A Prospective, Single-Center, Open-Label, Study of the Plasma Pharmacokinetics and Safety following a Single Drop and Twice-Daily Dosing for a Week of Topical Administration of Cetirizine Ophthalmic Solution, 0.24% in Healthy, Adult Subjects

Objective:

The objective of this study was to characterize the plasma pharmacokinetics and safety profile of 0.24% cetirizine ophthalmic solution following a single dose and twice daily (one week) dosing in healthy, adult subjects.

Study Design and Dosing:

This study was a prospective, single-center, open-label study that was conducted in healthy volunteers. All subjects underwent screening procedures and baseline safety evaluations at Visit 1 (Day -14 to -3). At Visit 2 (Day 1), enrolled subjects received one dose (1 drop) of study drug, which was instilled bilaterally by a trained staff technician. At Visit 3 (Day 2), subjects or their respective caregiver instilled one dose bilaterally under the observation of a trained staff technician, and an additional dose was instilled approximately eight hours after the first dose. Thereafter, subjects or their respective caregiver administered the study drug twice daily, bilaterally, approximately eight hours apart on Day 3 through Day 7. At Visit 4 (Day 8), the final dose of study drug was instilled bilaterally by a trained staff technician.

PK sampling:

Blood samples were collected at the following time points for measurement of plasma concentrations:

Visit 2 (Day 1): Within one hour pre-dosing and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 hours post-dose
Visit 3 (Day 2): At 24 hours after the single dose administered at Visit 2 (Day 1)
Visit 4 (Day 8): Within one hour pre- dosing and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 hours post-dose
Visit 5 (Day 9): At 24 hours after the single dose administered at Visit 4 (Day 8)

Pharmacokinetic Analysis:

Plasma samples were analyzed to determine concentrations of cetirizine using a validated assay method, with the quantification range of 0.1 - 100 ng/mL (See Section 4.1). The pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-24}, AUC_{∞}, $T_{½}$ and K_{el} were estimated by non-compartmental analysis utilizing WinNonlin (Pharsight Corporation, Version 5.0.1). With regard to the statistical analysis, the primary parameters of interest were the log-transformed estimates of AUC_{last} and C_{max}. In addition, accumulation ratios (R_{Cmax}, R_{AUC24}, and $R_{AUC\infty}$) were also calculated.

Pharmacokinetic Results:

From 25 subjects that were screened, 11 subjects were enrolled. Out of which, 10 completed the study and one subject was discontinued from the study prior to completion because of a lack of venous access. However, all subjects were included in the safety analysis. Mean mebendazole plasma concentration time-curves from both the treatment groups are presented in Figure 1. Descriptive statistics of pharmacokinetic parameters estimates are presented in Table 1. Following single and multiple doses of 0.24% cetirizine ophthalmic solution, plasma levels of cetirizine were detected in all dosed subjects. After single bilateral doses of 0.24% cetirizine ophthalmic solution, the mean C_{max} of cetirizine was 1.7 ng/mL and the mean time to maximum concentration was 2.2 hours. After a multiple bilateral doses, i.e., BID for a week, the mean C_{max} of cetirizine was 3.1 ng/mL and the mean time to maximum concentration was 1.6 hours. The terminal half-life of cetirizine was 8.6 hours after a single dose and 8.2 hours after multiple doses. After multiple bilateral doses, C_{max} was approximately 1.8 times higher than that observed following single bilateral doses.

Figure 1: Mean Cetirizine Plasma Concentration-Time Profiles **(source: Clinical Study Report 141000007, Figure 2)**

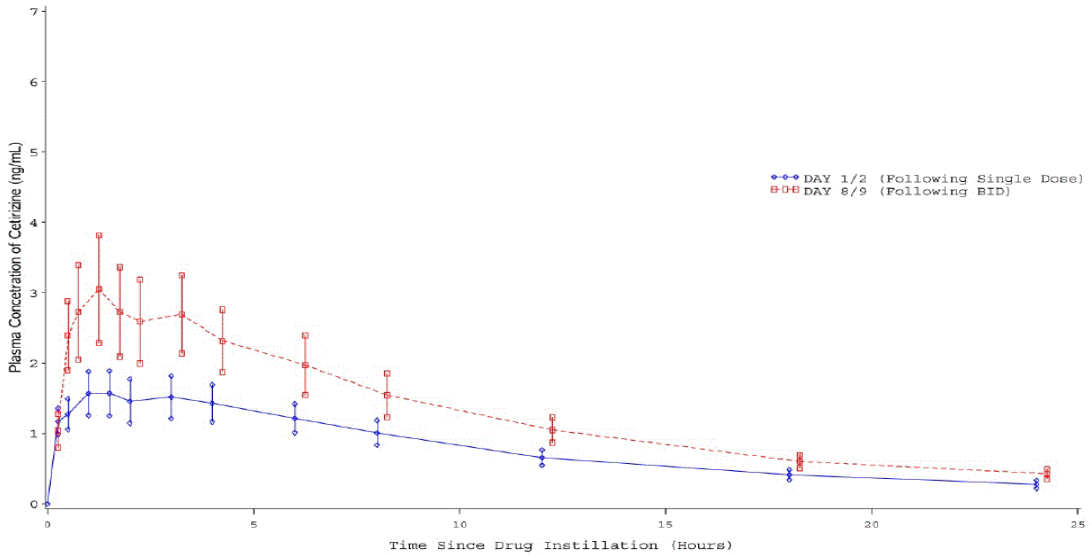

Table 1: Pharmacokinetic Parameter Estimates (source: Clinical Study Report 141000007, Table 10)

Parameter	Day 1/2	Day 8/9
Cetirizine 0.24 % (N=11)	Single dose	Multiple doses
C_{max} (ng/mL)		
N	10	10
Mean (SD)	1.690 (1.0004)	3.102 (1.99490)
95% CI of Mean	0.974, 2.406	1.676, 4.528
$AUC_{(0-24)}$ (ng·hr/ml)		
N	10	10
Mean (SD)	18.972 (10.4329)	31.688 (18.3170)
95% CI of Mean	11.508, 26.435	18.585, 44.791
$AUC_{(0-\infty)}$ (ng·hr/ml)		
N	10	10
Mean (SD)	22.453 (12.5063)	36.486 (20.3550)
95% CI of Mean	13.507, 31.400	21.925, 51.047
T_{max} (hours)		
N	10	10
Mean (SD)	2.200 (2.1628)	1.600 (1.5766)
95% CI of Mean	0.653, 3.747	0.471, 2.729
K_{el} ($hours^{-1}$)		
N	10	10
Mean (SD)	0.0842 (0.01797)	0.0867 (0.01282)
95% CI of Mean	0.0713, 0.0970	0.0775, 0.0958
$T_{½}$ (hours)		
N	10	10
Mean (SD)	8.591 (1.9172)	8.163 (1.2676)
95% CI of Mean	7.220, 9.963	7.256, 9.070
$RAUC_{(0-24)}$		
N		10
Mean (SD)		1.732 (0.5287)
95% CI of Mean		1.354, 2.110
$RAUC_{(0-\infty)}$		
N		10
Mean (SD)		1.773 (0.6841)
95% CI of Mean		1.284, 2.262
RC_{max}		
N		10
Mean (SD)		1.866 (0.5707)
95% CI of Mean		1.458, 2.275

1. Single dose = one drop in each eye. 2. Multiple doses = one drop in each eye twice daily for a week. CI=Confidence Interval.

Safety Results:

No deaths or other SAEs occurred in the study. There were no serious AEs or ocular TEAEs. Three non-ocular TEAEs of mild or moderate severity were reported, which were deemed not to be treatment related. Additionally, no clinically relevant mean change from baseline was reported for any of the safety parameters (visual acuity, slit-lamp biomicroscopy, dilated ophthalmoscopy, IOP, physical examination, vital signs, clinical laboratory measures) during this study.

Overall, the study drug was well tolerated and no safety issues were identified after the drug was topically administered to each eye BID for seven days.

Applicant's conclusion:

Study 14-100-0007 evaluated the pharmacokinetics and safety of 0.24% cetirizine ophthalmic solution. Plasma levels of cetirizine were detected in all subjects throughout the first 24 hours period following single and multiple dosing. After multiple doses, i.e., one drop in each eye BID for a week, C_{max} was approximately 1.8 times higher than that observed following a single dose. Overall, the mean C_{max} value was approximately 100 times lower than that observed following multiple oral doses of cetirizine, i.e., 10 mg tablets once daily for 10 days (Source: Zyrtec package insert).

There were no serious AEs or ocular TEAEs. Three non-ocular TEAEs of mild or moderate severity were reported, none of which were suspected to be treatment related. None of the TEAEs indicated a potential safety concern. Additionally, no clinically relevant mean change from baseline was reported for any of the safety parameters (visual acuity, slit-lamp biomicroscopy, dilated ophthalmoscopy, IOP, physical examination, vital signs, clinical laboratory measures) during this study.

The study drug was well tolerated and no safety issues were identified after the drug was topically administered to each eye twice daily for up to seven days.

Reviewer's assessment:

The Reviewer agrees with the Applicant's conclusions. In addition, it is noteworthy that as per the Zyrtec package insert, no plasma accumulation of cetirizine was observed following the multiple oral dose regimen of 10 mg QD x 10 days. Also, the PK of cetirizine was reported to be linear for oral Zyrtec doses ranging from 5 to 60 mg.

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/s/

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