CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208694Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action Including Original NDA and Resubmission

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA 208694
IND	IND 108558 [1]
Applicant	Nicox Ophthalmics, Inc. Previously Aciex Therapeutics, Inc.
Date of Submission	April 18, 2016
Complete Response Letter	October 7, 2016
Resubmission Class 2	March 8, 2017
PDUFA Goal Date	September 8, 2017
Review Type	Priority Submitted in response to Pediatric Written Request
Proprietary Name / Non-Proprietary Name	Zerviate cetirizine ophthalmic solution
Dosage Form(s) / Strength(s)	ophthalmic solution, 0.24%
Applicant Proposed Indication(s)/Population(s)	Treatment of ocular itching associated with allergic conjunctivitis in patients 2 years of age and older
Dosage Regimen	One drop in the affected eye(s) twice daily (8 hours apart during waking hours)
Action	*Approval*

[1] The applicant also has right of reference to IND (b) (4) (b) (4)

Material Reviewed/Consulted	**Names of discipline reviewers**
Medical Officer Review	Lucious Lim, William Boyd 9/26/2016, 5/16/2017
Statistical Review	Yunfan Deng, Yan Wang 9/16/2016
Pharmacology Toxicology Review	Andrew McDougal, Lori Kotch 9/17/2016, 5/11/2017
OPQ Review*	Chunchun Zhang, Haripada Sarker, Yushi Feng, Balajee Shanmugam, Brian Riley, Neal Sweeney, Elsbeth Chikhale, Banu Zolnik, Maotang Zhou, Sung Kim, Frank Wackes, Paul Perdue, Erin Andrews, Christina, Capacci-Daniel 9/23/2016, 5/15/2017
Clinical Pharmacology Review	Joshi Abhay Joshi, Phil Colangelo 9/29/2016
OSI	Roy Blay, Janice Pohlman, Susan Thompson 9/20/2016
CDTL Review	William Boyd 10/7/2016, 5/22/2017
Deputy Director Review	Wiley Chambers 10/7/2016
OSE/DMEPA Label Review	Leeza Rahimi, Hina Mehta 7/21/2016 Madhuri Patel, Sarah Vee 4/19/2017, 5/2/2017
DMEPA proprietary name review Proprietary name granted	Michelle Rutledge, Yelena Maslov 6/2/2016 Madhuri Patel, Sarah Vee 4/20/2017 Todd Bridges 4/28/2017
Pediatric Exclusivity	Matthew Bacho, Lynne Yao 9/29/2016
Pediatric Review Committee	Gettie Audain 9/16/2016
ADL	Jane Filie 5/24/2017
Project Manager	June Germain, Judit Milstein
505(b)(2) committee	MaryAnn Holovac email 10/4/2016, 5/2/2017

ADL=Associate Director for Labeling
OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP =Division of Medical Policy Programs
*OPQ review includes drug substance, drug product, manufacturing process, microbiology, facility and biopharmaceutics.

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1. Benefit-Risk Assessment

The review team recommends approval of NDA 208694 for the treatment of ocular itching associated with allergic conjunctivitis in patients 2 years of age and older. This recommendation is based on adequate nonclinical and clinical data as well as the successful resolution of the GMP deficiency identified in the Complete Response letter dated October 7, 2016.

Cetirizine is currently available in oral OTC products. It was previously available as an oral prescription product. Approval of this current application provides another treatment alternative for allergic conjunctivitis patients with itching.

2. Background

Cetirizine is a histamine H1 receptor antagonist, marketed by Johnson & Johnson under the trade name Zyrtec since December 1995 and available as on over-the-counter product since November 2007. The applicant conducted clinical studies, including study 14-100-0006 in pediatric patients as requested in the Pediatric Written Request issued September 15, 2015, reissued March 29, 2016. [2]

Cetirizine ophthalmic solution was developed under IND 108558. Sponsorship of the IND formally transferred from Aciex Therapeutics, Inc. to Nicox Ophthalmics, Inc. in March 2016. A pre-NDA meeting was held December 16, 2014, during which the clinical studies, nonclinical studies and format/content of the application were discussed and a separate pre-NDA CMC meeting was held February 19, 2015, to discuss manufacturing and product attributes. A meeting was held October 5, 2010, during which Aciex discussed the development of a (b) (4) ophthalmic solution (b) (4) On September 19, 2011, a second EOP2 meeting was held to discuss the clinical development plan for cetirizine ophthalmic solution, 0.24 % for the treatment of allergic conjunctivitis. On March 11, 2013, a Type C meeting was held to discuss the clinical program and expectations regarding the contents of the 505(b)(2) NDA.

The current NDA 208694 is submitted as a 505(b)(2) application, and Nicox relies on NDA 20346 for Zyrtec oral syrup as noted in the revised Form 356h, specifically for nonclinical information. While NDA 20346 has been withdrawn, it was not withdrawn for reasons of safety or efficacy.

The following products are approved for the treatment of ocular itching in patients with allergic conjunctivitis.

Trade Name	Active ingredient	NDA number

[2] See Pediatric Review Committee minutes by George Greeley, April 13, 2016 in DARRTS.

Alocril	nedocromil	21-009
Acular	ketorolac	19-700
Optivar	azelastine	21-127
Alamast	pemirolast	21-079
Pataday	(b) (4)	21-545
Elestat	epinastine	21-565
Bepreve	bepotastine besilate	22-288
(b) (4)	alcaftadine	22-134

The common side effects seen with topical histamine H1 receptor antagonists include: headache, asthenia, blurry vision, eye burning/stinging upon instillation, eye pain, cold/flu symptoms, cough, fatigue, dry eye, foreign body sensation, lid edema, keratitis, hyperemia, nausea, pharyngitis, pruritus, rhinitis, sinusitis, sore throat, and taste perversion, bitter taste.

Cetirizine ophthalmic solution 0.24% is not marketed in any country.

3. Product Quality/Facility Inspections

Overall, the Product Quality reviewers determined that satisfactory information and responses had been submitted to support the quality of the drug substance, drug product, biopharmaceutics and quality micro aspects of the application during the review of the original NDA and they remain acceptable. Furthermore, during the review of the Resubmission, the Office of Process and Facilities concluded the GMP deficiencies identified in the original NDA review have been addressed and resolved and the NDA is recommended for Approval.

A brief summary from the OPQ review is provided below.

Drug Substance
The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4) and the information is considered adequate from the OPQ perspective.

Drug Product
Cetirizine ophthalmic solution, 0.24% is a sterile, buffered, clear, colorless aqueous solution preserved with benzalkonium chloride 0.01% in a multi-dose ophthalmic low density polyethylene plastic dropper bottles with 2 presentations, a 5 mL fill in a 7.5 mL dropper bottle, or a 7.5 mL fill in a 10 mL dropper bottle, both with an LDPE plastic dropper tip and polypropylene cap.

The inactive ingredients also include edetate disodium, hypromellose, polyethylene glycol 400, and polysorbate 80, glycerin, sodium phosphate dibasic, hydrochloric acid/sodium hydroxide (to adjust pH); and water for injection. All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation.

The drug product specification includes tests for appearance, identification, assay, impurity, BAK, EDTA, particulate appearance, specific gravity, pH, osmolality, minimum fill, APHA

color, viscosity, particulate matter, and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Batch analyses are provided for 6 registration batches (3 batches for 5 mL fill in 7.5 mL bottle and 3 batches for 7.5 mL fill in 10 mL bottle) of drug products in the commercial container closure system at the commercial scale of (b) (4). All batches complied with the proposed specification.

The cetirizine drug product is a sterile, buffered, preserved, aqueous ophthalmic solution. The (b) (4)

The review notes that no bridging is necessary because the formulation used in the Phase 3 efficacy and safety studies, listed as AFH-002, is identical to the to-be-marketed formulation.

Additional stability data were submitted in the Resubmission which augment the information in the original NDA and support the requested shelf life of 30 months. The product can be stored at 15°C to 25°C (59°F to 77°F).

Inspections
During review of the original NDA, FDA field investigators found that the (b) (4) manufacturing facility for this application did not comply with the good manufacturing practice regulations in 21 CFR 210 and 211. The field investigators conveyed deficiencies to the representatives of this facility. During the review of the Resubmission, it was determined that there was satisfactory resolution of these deficiencies. The final recommendation is Approve, as stated in the Office of Process and Facilities review dated April 17, 2017.

The CMC review team recommends Approval of NDA 208694.

4. Nonclinical Pharmacology/Toxicology

As summarized by the Pharmacology/Toxicology reviewer in the review dated 5/11/2017, this 505(b)(2) application originally relied on NDA 19835 for Zyrtec® (cetirizine hydrochloride) tablets, and now relies on NDA 20346 - Zyrtec® (cetirizine hydrochloride) oral syrup. [See Section 11 regarding 505(b)(2)] Five nonclinical study reports for topical ocular cetirizine (tested alone or as a combination) were reviewed, including a study report for a 6-month topical ocular toxicity study in rabbits (report # AC170-157).

Applicant Study	Study Number	Study title

2307-001	2307-001	Ocular tissue distribution and melanin binding of [^{14}C]cetirizine in male rabbits following ocular administration
AC170-157	CB12-5018-O-TX	Six-month repeat-dose ocular toxicity study of cetirizine ophthalmic solution in Dutch-belted rabbits
AC170-083	PB0108003	14-day evaluation of the ocular toxicity of two ORA concentrations following multiple topical instillations in the eyes of New Zealand White rabbits
AC170-084	09-5210-G1	A 14-day ocular toxicity study of twice daily topical administration of cetirizine/fluticasone ophthalmic solution to Dutch-belted rabbits with a 14-day recovery period
AC170-156	CB12-5017-O-TX	Five-day ocular tolerability study of cetirizine hydrochloride ophthalmic solution in rabbits

Source: Pharmacology/Toxicology review

The systemic toxicokinetic (TK) results from this study show that exposure is substantially lower than systemic exposure from orally administered cetirizine.

Topical cetirizine ophthalmic solution, 0.24% was associated with hyperemia; this was also seen clinically and is described in the labeling under Section 6, Adverse Reactions. No clear adverse effects were observed in nonclinical studies. The ocular toxicology studies suggested that the drug product formulation may have slight effects (e.g. transient slight corneal fluorescein staining and increase in intraocular pressure). These findings were not observed clinically.

Cetirizine is an antihistamine drug. The current established pharmaceutical class (EPC) for cetirizine is "histamine-1 (H1) receptor antagonist". Affinity for other receptors has not been detected; and cetirizine has negligible anticholinergic and antiserotonergic activity. (b) (4)

At the request of CMC, two leachables (b) (4) were evaluated by the Pharmacology/ Toxicology reviewer who concluded there are no safety concerns for either leachable at the detected concentration levels. (documented in CMC review dated 5/15/2017; per email to CMC reviewer 5/10/2017).

The Pharmacology/Toxicology review team recommended approval as well as labeling revisions to Sections 8 and 13 which have been incorporated into the labeling.

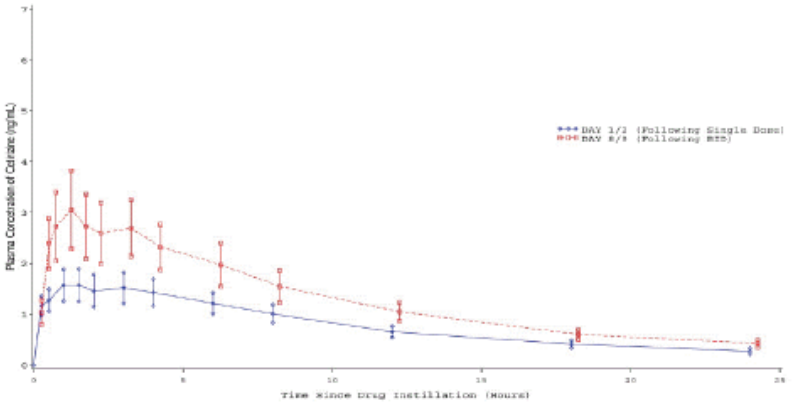
5. Clinical Pharmacology

The clinical pharmacology review notes that one pharmacokinetic study 14-100-0007 was conducted to assess the systemic exposure resulting from the repeated administration of 0.24% cetirizine ophthalmic solution. 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.

Systemic concentrations of cetirizine were detected in all subjects throughout the 24-hour period following single and multiple dosing in adults. 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 (C_{max} 3.1 ng/mL) than the reported mean C_{max} after multiple oral doses of cetirizine, i.e., 10 mg Zyrtec tablet QD for 10 days (C_{max} 311 ng/mL).

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 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.

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



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The Clinical Pharmacology review team recommends approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

During development, the applicant conducted seven clinical studies evaluating several formulations of cetirizine ophthalmic solution ranging from 0.05% to 0.24%.

For final formulation of cetirizine 0.24%, the first safety and efficacy pivotal study conducted was Study 11-100-0012 and followed by Study 12-100-0006. The duration-of-action evaluation time was 16 hours post study treatment in Study 11-100-0012; while it was 8 hours in Study 12-1000-0006. In the face-to-face meeting with the Division in March 2013, the agency commented that based on the summary information provided in the meeting package, it

appeared that the effect of cetirizine on ocular itching had worn off by 16 hours post-treatment and was only marginally effective 8 hours post-treatment; the Agency recommended that an additional study be conducted which demonstrates continued efficacy at 8 hours in order for cetirizine to be labeled as twice-daily (BID) dosing. Therefore, the applicant conducted an additional pivotal study (Study 13-100-0002) which evaluated duration of action for cetirizine at 8 hours posttreatment and sought the approval of cetirizine for BID dosing in this NDA submission.

In support of the present NDA, the Applicant submitted the following 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

Source: Clinical Pharmacology Review

The statistical reviewer summarized the efficacy of cetirizine ophthalmic solution, 0.24% evaluated in three pivotal studies: two multicenter studies 11-100-0012 and 13-100-0002, and one single-center study 12-100-0006. The three studies were randomized, double-masked, vehicle-controlled, parallel-group studies. They used the conjunctival allergen challenge (CAC) model to evaluate the onset and duration of action of cetirizine for the treatment of acute allergic conjunctivitis. These studies were almost identical in design except for the timing of duration-of-action evaluation. The onset of action was evaluated 15 minutes after study treatment instillation; and the duration of action was measured using CAC at 8 hours (in Studies 13-100-0002 and 12-100-0006) or 16 hours (in Study 11-100-0012) after study treatment instillation. The clinical review also summarized Study 11-100-0004.

The co-primary efficacy variables were ocular itching scores and conjunctival redness scores for these three studies. Ocular itching was subject-evaluated on a five-point scale (0 to 4, 0.5 unit increments were allowed) at 3, 5, and 7 minutes post CAC; and conjunctival redness was

investigator-evaluated on a five-point scale (0 to 4, 0.5 unit increments were allowed) at 7, 15, and 20 minutes post CAC.

The primary efficacy analyses were conducted on the intent-to-treat (ITT) population with last observation carried forward (LOCF) for missing data using analysis of covariance (ANCOVA) models. The models were run at each post-CAC time point at Visits 3B and 4, with the average of the subjects' post-CAC scores at Visit 2 (Day -14) included as a covariate. Cetirizine was compared to vehicle, and least squares means (LS Means) and the corresponding 95% confidence intervals were provided.

Ocular Itching

For the primary efficacy endpoint of ocular itching scores, the three studies demonstrated statistical superiority of cetirizine to vehicle at both the onset and duration-of-action evaluations.

Summary of Ocular Itching Scores (Intent-to-Treat [ITT], Last Observation Carried Forward [LOCF])

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score Time Post-CAC			Treatment Difference (95% CI)[1] p-value[2] Time Post-CAC		
				3 min	5 min	7 min	3 min	5 min	7 min
11-100-0012	**Cetirizine**	**46/44**	**15 min**	0.71	1.01	1.00	-1.47 (-1.82, -1.12) <0.0001	-1.31 (-1.66, -0.95) <0.0001	-1.10 (-1.48, -0.72) <0.0001
	Vehicle	**45/45**		2.18	2.31	2.10			
	Cetirizine	**46/44**	**16 hours**	1.71	1.88	1.76	-0.64 (-0.95, -0.33) 0.0003	-0.62 (-0.95, -0.29) 0.0004	-0.46 (-0.84, -0.08) 0.0184
	Vehicle	**45/45**		2.34	2.50	2.22			
12-100-0006	**Cetirizine**	**50/49**	**15 min**	1.00	1.18	1.11	-1.38 (-1.72, -1.05) <0.0001	-1.25 (-1.58, -0.91) <0.0001	-1.00 (-1.35, -0.65) <0.0001
	Vehicle	**50/47**		2.38	2.43	2.11			
	Cetirizine	**50/49**	**8 hours**	1.76	1.85	1.54	-0.93 (-1.26, -0.61) <0.0001	-0.89 (-1.24, -0.54) <0.0001	-0.99 (-1.40, -0.59) <0.0001
	Vehicle	**50/47**		2.69	2.74	2.53			
13-100-0002	**Cetirizine**	**51/43**	**15 min**	1.01	1.17	1.15	-1.53 (-1.92, -1.15) <0.0001	-1.34 (-1.71, -0.97) <0.0001	-1.07 (-1.46, -0.69) <0.0001
	Vehicle	**50/44**		2.54	2.51	2.23			
	Cetirizine	**51/43**	**8 hours**	1.94	2.03	1.82	-0.92 (-1.25, -0.58) <0.0001	-0.90 (-1.23, -0.57) <0.0001	-0.84 (-1.21, -0.48) <0.0001
	Vehicle	**50/44**		2.86	2.94	2.66			

* Post study treatment instillation.
[1] Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.
[2] P-value calculated using a two-sample t-test comparing active treatment to vehicle at each individual time point.
Source: Table 5 of Summary of Clinical Efficacy, Table 9 of Study 11-100-0012 Report, Table 9 of Study 12-100-0006 Report, and Tables 9 and 10 of Study 13-100-0002 Report.
Source of Table: Statistical Review of NDA 208694

At the 15-minute onset-of-action evaluation, the mean itching score for cetirizine ranged from 0.71 to 1.18, and for vehicle ranged from 2.10 to 2.54; the treatment difference ranged from -1.00 to -1.53 with p-values <0.0001 at each of the post-CAC time point (3-, 5-, and 7-minute).

At the 8-hour duration-of-action evaluation, the mean itching score for cetirizine ranged from 1.54 to 2.03, and for the vehicle ranged from 2.53 to 2.94; the treatment difference ranged from - 0.84 to -0.99 with p-values <0.0001 at each of the post-CAC time point.

At the 16-hour duration-of-action evaluation, the mean itching score for cetirizine ranged from 1.71 to 1.88, and for the vehicle ranged from 2.22 to 2.50; the treatment difference ranged from -0.46 to -0.64 with p-values <0.0184 for at each of the post-CAC time point.

In order to demonstrate clinical significance in a CAC study, the difference between groups should be at least one unit on a scale from 0-4 at a majority of the time points evaluated at the time of onset of the drug product's effect. This criterion for the endpoint of ocular itching was demonstrated in studies 11-100-0004, 11-100-0012, 12-100-0006, and 13-100-0002.

Conjunctival Redness

For the primary efficacy endpoint of conjunctival redness scores, the three studies 11-100-0012, 12-100-0006 and 13-100-0002 failed to demonstrate statistical superiority of cetirizine to vehicle at both the onset and duration-of-action evaluations.

Summary of Conjunctival Redness Scores (ITT, LOCF)

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score Time Post-CAC			Treatment Difference (95% CI)[1] Time Post-CAC		
				7 min	15 min	20 min	7 min	15 min	20 min
11-100-0012	Cetirizine	46/44	15 min	2.02	2.23	2.28	-0.03 (-0.34, 0.27)	0.09 (-0.20, 0.39)	0.10 (-0.19, 0.40)
	Vehicle	45/45		2.05	2.13	2.18			
	Cetirizine	46/44	16 hours	1.72	1.96	1.92	-0.22 (-0.55, 0.11)	-0.06 (-0.39, 0.27)	-0.06 (-0.38, 0.26)
	Vehicle	45/45		1.94	2.02	1.98			
12-100-0006	Cetirizine	50/49	15 min	1.66	1.93	1.95	-0.33 (-0.53, -0.06)	-0.03 (-0.26, 0.19)	-0.01 (-0.26, 0.23)
	Vehicle	50/47		1.98	2.09	2.09			
	Cetirizine	50/49	8 hours	1.97	2.30	2.30	-0.30 (-0.53, -0.06)	-0.03 (-0.26, 0.19)	-0.01 (-0.26, 0.23)
	Vehicle	50/47		2.27	2.34	2.32			
13-100-0002	Cetirizine	51/43	15 min	1.92	2.19	2.15	-0.46 (-0.73, -0.19)	-0.18 (-0.43, 0.07)	-0.25 (-0.51, 0.00)
	Vehicle	50/44		2.38	2.37	2.41			
	Cetirizine	51/43	8 hours	1.97	2.13	2.09	-0.42 (-0.68, -0.16)	-0.24 (-0.49, 0.00)	-0.31 (-0.58, -0.05)
	Vehicle	50/44		2.39	2.38	2.40			

* Post study treatment instillation.
[1] Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.
Source: Table 6 of Summary of Clinical Efficacy in the Statistical Review of NDA 208694

The statistical reviewer note that if the applicant had split the 0.05 alpha level between the two co-primary efficacy endpoints (0.025 alpha level for ocular itching scores and 0.025 alpha level for conjunctival redness scores), all three studies would still have had demonstrated statistical superiority of cetirizine to vehicle at each post-CAC time point (3, 5, and 7 minutes) for the onset- and duration-of-action visits in ocular itching scores (all p-values < 0.025), as seen based on the p-values of ocular itching scores in the Table above.

The clinical reviewers and statistical reviewers recommend approval. Noting that, a clinically significant duration of effect on ocular itching was not demonstrated at 16 or 24 hours in studies, 11-100-0004, or 11-100-0012, but duration of 8 hours was marginally demonstrated in studies 12-100-0006, and 13-100-0002, the results of the latter two will be included in labeling.

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	2.94
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	1.82	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.
* $p<0.05$

(b) (4)

8. Safety

All patients who were enrolled and received drug in the following seven studies were evaluated for safety: 11-1000-004, 11-100-012; 11-100-0013; 12-100-006; 13-100-002, 14-100-006 and 14-100-007. The medical officer notes that adverse reactions were pooled from these seven studies because each study evaluated the 0.24% concentration of cetirizine, the proposed to-be-marketed dose strength. There were 554 patients exposed to cetirizine 0.24% (514 patients in to-be-marketed formulation studies, 40 patients to other 0.24% formulations) and 341 patients received vehicle.

There were no deaths in the studies; 4 cetirizine and 5 vehicle patients discontinued study for various reasons. One (0.2%) subject in the cetirizine group developed non-ocular herpes zoster and 1 (0.3%) subject in the vehicle group reported anaphylactic shock and withdrew.

The most frequent ocular adverse reactions were conjunctival hyperemia (5%), instillation site pain (4%) and ocular hyperemia (2%). There were no non-ocular adverse reactions that occurred at a frequency of ≥ 1 %, as shown in the table below.

System Organ Class (SOC) Preferred Term (PT)	**Cetirizine 0.24% Final Formulation (N=511)**	**Cetirizine 0.24% 'Other' Formulation (N=40)**	**Total Cetirizine 0.24% (N=551)**	**Vehicle (N=329)**	**All Subjects (N=880)**
OCULAR	N (%)	N (%)	N (%)	N (%)	N (%)
Eye Disorders					
Conjunctival hyperemia	27 (5.3)	0 (0.0)	27 (4.9)	19 (5.8)	46 (5.2)
Ocular hyperemia	10 (2.0)	0 (0.0)	10 (1.8)	3 (0.9)	13 (1.5)
Visual acuity reduced	3 (0.6)	0 (0.0)	3 (0.5)	7 (2.1)	10 (1.1)
General Disorders and Administration Site Conditions					
Instillation site pain	20 (3.9)	0 (0.0)	20 (3.6)	3 (0.9)	23 (2.6)

Studies 11-100-0012 and Study 12-100-0006 enrolled pediatric patients above 10 years of age. Study 13-100-0002 enrolled patients 18 years and older.

The applicant also conducted a multi-center, double-masked, randomized, vehicle-controlled, parallel-group safety study (Study 14-100-0006) to evaluate the safety of cetirizine ophthalmic solution, 0.24% used twice daily in healthy adult subjects and in 59 pediatric subjects age ≥2 years to ≤ 10 years with a history or family history of atopic disease (including allergic conjunctivitis). Cetirizine ophthalmic solution, 0.24% was found to be safe and well-tolerated in the pediatric population, 2 to10 years of age with no unexpected safety issues. Five treatment emergent adverse events (TEAEs) were reported in the pediatric population. Conjunctival hyperemia occurred in 1 subject (1.7%) in the vehicle treatment group. The other 4 TEAEs were non-ocular and occurred in 4 subjects (6.8%), 3 were reported in the cetirizine group (2 events of otitis media and 1 event of hand foot and mouth disease) and 1 TEAE of sunburn was reported by a subject in the vehicle group. No pediatric subject discontinued from the study due to a TEAE. Since this study investigated the safety of cetirizine in pediatric subjects as young as 2 years old, and was conducted in response to a Pediatric Written Request, the NDA was reviewed as a Priority.

A 120 Day Safety Update was received on August 8, 2016 and reported an additional ongoing clinical safety trial (Study 15-100- 0010) to evaluate the safety of cetirizine ophthalmic solution 0.24% dosed three times a day (TID) in adults and pediatric subjects. Except for the dosing regimen, the study design was identical to safety Study 14-100-006 BID dosing).

Study 15-100-0010 was completed August 8, 2016. The safety profile of cetirizine ophthalmic solution, 0.24% observed in Study 15-100-0010 was similar to that observed in Study 14-100-006. The majority of TEAEs in both trials were ocular and within the SOC Eye Disorders. Although similar in nature, the reported rate of ocular TEAEs in Study 15-100-0010 was lower than in Study 14-100-0006. This observation was considered attributable to the variables that arise while conducting clinical trials: different subjects, different investigators, and conducting studies at different times of the year.

In Study 15-100-0010, there were no new TEAEs of concern or an increase in the frequency of the most commonly reported TEAEs (hyperemia, instillation site pain, visual acuity reduced)

observed previously with cetirizine ophthalmic solution, 0.24% or its vehicle and as proposed in the package insert.

In order to identify any additional safety information pertaining to the clinical use of cetirizine from that reported previously in the 120 Day Safety Update, a thorough literature search was conducted (review period: 01 Jul 2016 – 31 Dec 2016) and data from the FDA Adverse Event Reporting System (FAERS) was reviewed (review period: Q4-2015 to Q3-2016). No new safety information was identified relevant to topical ophthalmic dosing.

The reviewers recommend approval; the benefits of the product outweigh risks.

9. Advisory Committee Meeting

This application did not raise new scientific issues that needed input from the Advisory Committee.

10. Pediatrics

The application was submitted in response to a Pediatric Written Request and included pediatric patients between 2 to 17 years of age. The applicant was granted pediatric exclusivity on August 29, 2016. The Pediatric Review Committee agreed that the product is fully assessed for patients 2 years and older, and agreed with the Division to grant a partial waiver in patients from birth to less than 2 years old because the product fails to represent a meaningful therapeutic benefit and unlikely to be used patients < 2 years.

11. Other Relevant Regulatory Issues

Post-Action Teleconference
Following receipt of the Complete Response letter, the Applicant held a teleconference with the Division on November 21, 2016 (Minutes dated 12/9/2016) during which how to address the CMC deficiency, labeling and resubmission were discussed.

505(b)(2)
This is a 505(b)(2) application and has been cleared for action by the 505(b)(2) committee as communicated via email by Mary Ann Holovac on October 4, 2016 and May 2, 2017. The following information will be included in the 505(b)(2) assessment form:

With respect to Pharmacology/Toxicology:
"Essentially the Sponsor provided original data and cross-referenced data to support the application, and relied upon a listed drug (Zyrtec®) to fill in the gaps. Although published data were provided, they were not needed to support approval. We concluded that the relied upon safety data was adequately bridged and recommended approval."

The Applicant has submitted a study report for a 6-month topical ocular toxicity study in

rabbits (report # AC170-157). The systemic toxicokinetic (TK) results from this study show that exposure is substantially lower than systemic exposure from orally administered cetirizine.

As documented in the Pharmacology/Toxicology review (dated 5/11/2017), for the April 18, 2016 NDA submission, the Applicant relied on NDA 19835 - Zyrtec® (cetirizine hydrochloride) tablets. The Office of New Drugs 505(b)(2) Committee advised the Division that for NDA 208694 the appropriate listed drug product is NDA 20346, Zyrtec® (cetirizine hydrochloride) oral syrup. Thus in the March 8, 2017 resubmission, the Applicant relies on NDA 20346, no longer listing NDA 19835.

With respect to Clinical Pharmacology:
This is also consistent with the human PK data following the different routes of administration. Systemic levels achieved after topical ocular exposures are significantly lower (100 fold) than seen after oral exposure.

With respect to Clinical Studies of safety and efficacy:
The application is not a 505(b)(2) from the clinical studies perspective. The clinical safety and efficacy data do not rely on Zyrtec, nor does the applicant make a comparison to Zyrtec. The applicant performed their own clinical studies with the to-be- marketed product. These studies support the safety and efficacy of the product.

OSI Inspection Two relatively large sites from Protocols 14-100-0006 and 11-100-0012 were inspected and both were classified as NAI. OSI concluded the study data are acceptable to support the application.

12. Labeling

Labeling has been reviewed by the Division, including the Associate Director for Labeling (ADL), and consultants.

- **Package Insert:** Labeling has been finalized and the ADL has confirmed the labeling is consistent with PLR and PLLR.
- **Carton and Container:** The Division of Medication Errors Product Assessment reviewed the proposed carton labeling, bottle label and prescribing information. DMEPA provided recommendations that were incorporated in labels.
- **Trade Name:** DMEPA concluded that the proposed proprietary name, Zerviate, was conditionally acceptable and communicated this to the applicant in a letter dated 6/15/2016 and granted on 4/28/2017.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies: Not applicable
- Other Postmarketing Requirements and Commitments: Not applicable

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
05/29/2017