CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208694Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 18, 2017
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208694
Applicant	Nicox Ophthalmics, Inc.
Date of Submission	March 8, 2017
PDUFA Goal Date	September 8, 2017
Proprietary Name / Established (USAN) names	Zerviate (cetirizine ophthalmic solution) 0.24%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of ocular itching associated with allergic conjunctivitis
Recommended:	Approval

1. Introduction

Submitted is an amendment addressing the Complete Response (CR) received by the applicant on October 7, 2016, for NDA 20869, Zerviate (cetirizine ophthalmic solution) 0.24%. The original NDA was submitted on April 18, 2016. Applicant 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.

This NDA was originally filed under the 505(b)(2) pathway, listing NDA 19-835 for Zyrtec (cetirizine hydrochloride) tablets as the reference listed drug. The Office of New Drugs (OND) Clearance Committee advised DTOP that for NDA 208694, the appropriate listed drug product is NDA 020346 -Zyrtec® (cetirizine hydrochloride) oral syrup. For the 3/08/2017 submission, the Applicant is no longer listing NDA 019835, and instead is listing NDA 020346. The Division had no objection to this change in the listed drug product. FDA's website has published one label for both NDA 19835 and NDA 203461; the findings of safety and efficacy are the same for both.

Cetirizine is an antihistimine (H1-receptor antagonist) that has been developed for the treatment of ocular itching associated with allergic conjunctivitis.

Cetirizine, in oral dose formulation (Zyrtec) was approved in the United States to treat seasonal and perennial allergic rhinitis, as well as idiopathic urticarial in patients 12 years of age and older in 1995. In 2007, Zyrtec was approved for over-the-counter use.

Adverse events for this class of drugs (topical H1 antagonists) are well known. Common adverse events commonly reported in clinical trials with this class 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, phayrngitis, pruritis, rhinitis, sinusitis, sore throat, and taster perversion/bitter taste.

The Agency issued a Written Request for Cetirizine Ophthalmic Solution, 0.24% on September 15, 2015, amended on March 29, 2016. The Written Request identified the need for pediatric safety information specific to Cetirizine Ophthalmic Solution, 0.24% and included the Agency's agreement with the protocol and statistical analysis plan for Study 14-100-0006, a double masked, randomized, vehicle-controlled, parallel-group study evaluating the safety of Cetirizine Ophthalmic Solution, 0.24% in adults and pediatric patients 2 to 17 years of age. The report for Study 14-100-0006 is included in this application. The report was found to meet the terms of the Written Request on August 29, 2016.

See CDTL memo dated 10/7/2016 in DARRTS.

2. Background

On March 10, 2008, a Pre-IND meeting was held for the clinical development plan for cetirizine ophthalmic solution, 0.24% (Pre-IND (b) (4).

The clinical development program for topical ophthalmic cetirizine was initiated by a physician sponsored investigational new drug application for a (b) (4). The applicant, Nicox, filed an original IND for a cetirizine fluticasone combination product (IND 108,558). IND (b) (4) was cross referenced in the initial filing of IND 108,558.

On October 5, 2010, an End-of-Phase 2 (EOP2) meeting (IND 108558) was held to discuss the clinical development program for the (b) (4) (b) (4) for the treatment of allergic conjunctivitis. The (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 December 16, 2014, a Pre-NDA meeting was held to discuss the content and format of the planned 505(b)(2) NDA for cetirizine ophthalmic solution, 0.24% for the treatment of ocular itching associated with allergic conjunctivitis.

Approved Drugs for Indication of Ocular Itching

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

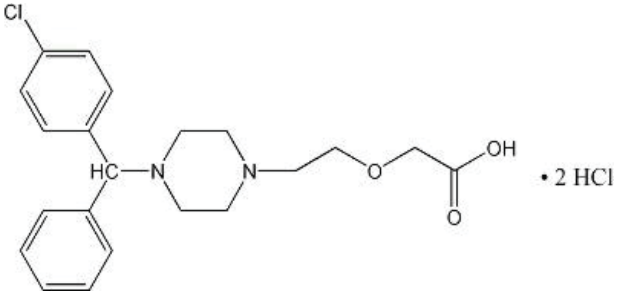
3. Product Quality

See CDTL memo dated 10/7/2016 in DARRTS.

See the Office of Product Quality Review dated 9/23/16:

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 $C_{21}H_{25}ClN_2O_3$•2HCl.

Chemical Structure:



Recommended International Nonproprietary Name (INN): Cetirizine Dihydrochloride

Compendial Names:
Cetirizine Hydrochloride (United States Pharmacopeia)
Cetirizine Dihydrochloride (European Pharmacopoeia)

Chemical Name
(RS)-2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid

Dihydrochloride

Release Specification of the Drug Substance:

Table 3.2.S.4.1-1. Release Specification for Cetirizine Dihydrochloride	
Test	**Acceptance Criteria**
Appearance	White crystalline powder
Identification IR	 Positive
Melting point	(b) (4)
pH	1.2 to 1.8
Clarity and color	(b) (4)
Specific rotation	
Heavy metals	NMT (b) (4) ppm
Loss on Drying	NMT 0.5%
(b) (4)	NMT (b) (4) %
Assay $HClO_4$ Titration HPLC	 (b) (4) (b) (4)
Foreign substances	NMT (b) (4) ppm
Bulk density	Report results
Tapped density	Report results
Particle size D[0.5] D[0.9]	 Report results Report results
Residual solvents	
(b) (4)	NMT (b) (4) ppm
	NMT (b) (4) %
	NMT %
	NMT %
	NMT %
	NMT %
	NMT %

Table 3.2.S.4.1-1. Release Specification for Cetirizine Dihydrochloride			
(b) (4)	NMT	(b) (4)	
Ceti2 (Cetirizine Ethanol)	NMT		
(b) (4)	NMT		
	NMT		
	NMT		
	NMT		
	NMT		
	NMT		
	NMT		
	NMT		
	NMT		
Desethoxycetirizine (Cetirizine acetic acid)	NMT		
(b) (4)	NMT		
	NMT		
	NMT		
	NMT		
	NMT		
Total related substances	NMT		
EP = European Pharmacopeia; HPLC = high-performance liquid chromatography; IR = infrared; NMT = not more than; USP = United States Pharmacopeia.			

Source: Module 3.2.S.4.1

Description and Composition of the Drug Product

Table 3.2.P.1-1. Components and Concentrations of Cetirizine Ophthalmic Solution, 0.24%, Formulation				
Component	**Function**	**Reference to Quality Standards**	**Concentration (mg/mL)**	**Quantity (mg) Per Bottle 7.5-cc[c]/10-cc[d]**
Cetirizine (b) (4) [a]	Active	USP/Ph Eur Certificate of analysis, *Section 3.2.S.4.1*	2.85 (2.40 as cetirizine (b) (4)	12.0/18.0 (cetirizine (b) (4)
Benzalkonium chloride	(b) (4) preservative	USP/NF	(b) (4)	
Glycerin	(b) (4)	USP/NF		

Sodium phosphate, dibasic [redacted]	[redacted]	USP/NF	[redacted]
Edetate disodium, [redacted]		USP/NF	
Polyethylene glycol 400		USP/NF	
Polysorbate 80		USP/NF	
Hypromellose		USP/NF	
[redacted] Sodium hydroxide[b]	pH adjustment	USP/NF/Ph Eur	
[redacted] Hydrochloric acid[b]	pH adjustment	USP/NF/Ph Eur	
Water for injection	[redacted]	USP/NF	

NF = National Formulary; Ph Eur = European Pharmacopoeia; *qs* = quantity sufficient;
USP = United States Pharmacopeia.
a = Also known as Cetirizine hydrochloride, USP

[redacted]

Release Specification of the Drug Product:

Table 3.2.P.5.1-1. Specification for Cetirizine Ophthalmic Solution, 0.24%

Test	Acceptance Criterion	Analytical Procedure Reference
Product appearance	Clear, colorless solution	Visual
Cetirizine assay [redacted]	NLT [redacted]% and NMT [redacted]%	HPLC (ATM 189)
Cetirizine related impurities	[redacted]	HPLC (ATM 171)
Benzalkonium chloride [redacted]	NLT [redacted]% and NMT [redacted]% LC	HPLC (ATM 188)
Edetate disodium [redacted]	NLT [redacted]% and NMT [redacted]% LC	HPLC (ATM 190)

Table 3.2.P.5.1-1. Specification for Cetirizine Ophthalmic Solution, 0.24%		
Identification 1	Compare the chromatogram of sample solution to that of the standard solution. The retention time of cetirizine peak from the standard solution should be within ± (b) (4) % of the retention time of cetirizine peak from the standard.	HPLC (ATM 189)
Identification 2	Using a suitable instrument, collect the spectra for sample solution and standard solution from 190 nm and 400 nm. The main UV maxima found in the sample solution should be within (b) (4) of the main UV maxima found in the standard solution.	HPLC (ATM 189)
Particulate appearance	The solution is free from visible particulates	Visual
Specific gravity	(b) (4) at 25°C	USP <841>
pH	pH (b) (4)	USP <791>
Osmolality	(b) (4) mOsm/kg	USP <785>
Minimum fill	Meets USP requirements	USP <755>
APHA color	NMT (b) (4) APHA Units	XS-31799
Viscosity	(b) (4) cps	XS-31799
Sterility	Meet the USP requirements	USP <71>
Particulate matter	NMT (b) (4) particles/ mL ≥10 µm NMT (b) (4) particles/ mL ≥25 µm NMT (b) (4) particles mL ≥50 µm	USP <789>
HPLC = high-performance liquid chromatography; LC = label claim; NLT = not less than; NMT = not more than; USP = United States Pharmacopeia.		

Source: Module 3.2.P.5.1

Drug Product Container Closure

Cetirizine Ophthalmic Solution, 0.24% is provided in 2 presentations, both of which consist of a white low-density polyethylene (LDPE) bottle, a natural color LDPE dropper tip, and a white polypropylene (PP) (b) (4) closure.

One presentation is 5 mL of Cetirizine Ophthalmic Solution, 0.24% filled into a 7.5-cc LDPE bottle (b) (4). The second presentation is 7.5 mL of Cetirizine Ophthalmic Solution, 0.24% filled into a 10-cc LDPE bottle (b) (4)

(b) (4). Both presentations have a shrink-wrap tamper-resistant band around the bottle cap applied during manufacture.

Table 3.2.P.7-1. Container Closure Components Sourcing

Component	(b) (4) Manufacturer/Site	Associated DMFs
7.5-cc (b) (4) LDPE bottle and 10-cc (b) (4) LDPE bottle	(b) (4)	(b) (4)
7.5-cc Bottle: (b) (4)	(b) (4)	
and 10-cc Bottle: (b) (4)	(b) (4)	

LDPE = low-density polyethylene; PP = polyethylene.

Source: Module 3.2.P.7.1

From the Office of Product Quality Review dated 5/15/17:

The original NDA was issued a Complete Response due to the outcome of an inspection of the drug substance manufacturing facility. All other aspects of the product quality review were deemed acceptable.

Inspections

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 17-Apr-2017.

Drug Substance

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)			Current Site Compliance Status	Approve

(b) (4)

Second Review Cycle: The compliance review for this firm at the time of the original PDUFA Goal Date recommended a "Withhold." The firm's compliance status has now been changed to be acceptable.

The last comprehensive CGMP inspection was completed on (b) (4) The firm is a manufacturer of APIs by chemical synthesis for human and animal drug products. The APIs are intended to be further manufactured into sterile injectable, non-sterile and OTC drug products. This inspection utilized the systems approach and covered all systems and was conducted for profile class CSN. At the conclusion of the inspection, a 13 item FDA 483 was issued. The firm was classified initially by the ORA inspectional team as "Official Action Indicated – OAI"; and was subsequently evaluated by CDER (refer to (b) (4) (b) (4) where the surveillance/CGMP inspection final classification was downgraded to Voluntary Action Indicated. This decision was based upon OMQ's review of the EIR, FDA Form 483, pertinent exhibits, additional information received via a teleconference, and the firm's response, we believe CGMP deviations for the manufacturing of API exist. These deviations were discussed with firm management via a teleconference on 11/21/16. Items discussed during the call were as follows: (b) (4)

Therefore, the Facility is considered acceptable for the intended operations stated in NDA 208694 based upon review of the completed inspection.

There is no requirement for post-approval or surveillance coverage at this time.

Drug Product

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
Akorn, Inc. 72-6 Veronica Ave, Somerset, New Jersey, USA, 08873	2246848	SLQ / Drug product manufacturing, packaging, stability testing, release testing	**Previous Inspectional History**	**Approve (after file review and IR response)**

Recommendation and Conclusion on Approvability from OPQ

Drug substance, process, quality micro and biopharmaceutics reviewers have recommended approval of the NDA as documented in Review #1 dated 23-Sep-2016.

As documented in this resubmission Review #2, all drug product issues have been satisfactorily resolved. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 17-Apr-2017.

Therefore, NDA 208694 is recommended for approval from Product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

See the Nonclinical Pharmacology/Toxicology Review dated 9/17/16.

From the Nonclinical Pharmacology/Toxicology Review dated 5/11/17:

A Complete Response was issued on October 7, 2016 for reasons unrelated to the supporting nonclinical data. The original NDA was approvable from a nonclinical Pharmacology/Toxicology (P/T) perspective (McDougal, 9/17/2016, NDA 208694).

The Applicant submitted a Resubmission – Complete Response Amendment on March 8, 2017. For the 4/18/2016, submission, the Applicant had listed NDA 019835 - Zyrtec® (cetirizine hydrochloride) tablets. The Office of New Drugs (OND) Clearance Committee advised DTOP that for NDA 208694, the appropriate listed drug product is NDA 020346 -Zyrtec® (cetirizine hydrochloride) oral syrup. For the 3/08/2017 submission, the Applicant is no longer listing NDA 019835, and instead is listing NDA 020346. P/T has no objection to this change in the listed drug product. FDA's website has published one label for both NDA 19835 and NDA 203461; the findings of safety and efficacy are the same for both.

5. Clinical Pharmacology/Biopharmaceutics

See the original Clinical Pharmacology review dated 9/29/16.

6. Sterility Assurance

See original Office of Product Quality Review, Microbiology subsection, dated 9/23/16.

7. Clinical/Statistical- Efficacy

See the original Medical Officer Review dated 9/26/16.

Efficacy Summary Statement

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.

A clinically significant duration of effect 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. A clinical effect on conjunctival redness was not demonstrated in any of the four studies.

8. Safety

See the original Medical Officer Review dated 9/26/16.

Safety Summary Statement

Adequate and well controlled studies support the safety of Zerviate (cetirizine ophthalmic solution) 0.24% for the treatment of ocular itching associated with allergic conjunctivitis. The most ocular common adverse events were conjunctival hyperemia (5%), instillation site pain (4%), and ocular hyperemia (2%). (b) (4) All non-ocular adverse events occurred in <1% of subjects in both treatment groups.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

This drug was tested in a pediatric population. Safety and efficacy of cetirizine ophthalmic solution have not been established in pediatric patients less than 2 years of age because the diagnosis of allergic conjunctivitis cannot be reliably made in patients of this age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in patients greater than 10 years of age because: 1) there are no differences in the clinical characteristics or course of the disease at any age, and 2) patients below the age of 10 cannot provide reliable assessments of itching.

The Agency issued a Written Request for Cetirizine Ophthalmic Solution, 0.24% on September 15, 2015. The Written Request identified the need for pediatric safety information specific to cetirizine and included the Agency's agreement with the protocol and statistical analysis plan for Study 14-100-0006, a double masked, randomized, vehicle-controlled, parallel-group study evaluating the safety of Cetirizine Ophthalmic Solution, 0.24% in adults and pediatric patients 2 to 17 years of age. The Agency amended the Written Request on March 29, 2016. According to the Amended Written Request, the report for Study 14-100-0006 was to be submitted to the Agency on or before July 31, 2016. The report for Study 14-100-0006 is included in this application. Prior to this application, Nicox Ophthalmics, Inc. (Nicox) had not submitted this report to the Agency.

This application was placed on the schedule of the Pediatric Exclusivity Board for August 23, 2016. The Board granted exclusivity on August 29, 2016.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
See the original Biostatistics review dated 9/16/16.

The statistical reviewer concluded that (b) (4) there was substantial statistical evidence to support the superiority of cetirizine to vehicle in terms of ocular itching scores.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Zerviate, and granted conditional acceptance on 4/28/16. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA completed a formal review of the package insert and container labeling on 7/21/16 and found the revised package insert and carton and container labeling acceptable.

DMEPA completed a review of the re-submitted proprietary name risk assessment and did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

FINANCIAL DISCLOSURE

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

OSI

A routine Office of Scientific Investigations (OSI) audit was requested.

Per the OSI review dated 9/20/16:

The Applicant submitted this NDA to support the use of Zerviate for the treatment of ocular itching associated with allergic conjunctivitis. The following two protocols were inspected in support of this application.

Protocol 14-100-0006 was entitled "A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of Cetirizine 0.24% Ophthalmic Solution Used Twice Daily in Healthy Adult Subjects and in Pediatric Subjects with a History or Family History of Atopic Disease (including Allergic Conjunctivitis)", and Protocol 11-100-0012 was entitled "A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Cetirizine 0.24% Ophthalmic Solution (Formula AFH-002) Compared to Vehicle (Formula AFH-001) in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis".

The sites of Drs. DeCastro and Ackerman were selected because they included relatively large enrollments for the study.

RESULTS (by Site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
1/ Dawn DeCastro, M.D. Andover Eye Associates 138 Haverhill Street Andover, MA 01810	14-100-0006/ 154	1-6 Sep 2016	NAI. Pending final classification.
2/ Stacey Ackerman, M.D. Philadelphia Eye Associates 1703 S. Broad Street Philadelphia, PA 19148	11-100-0012/ 36	15-17 Aug 2016	NAI.

Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

The studies appear to have been conducted adequately, and the data generated by each of each of these sites appear acceptable in support of the respective indication.

12. Labeling

NDA 208694 Zerviate (cetirizine ophthalmic solution) 0.24% is recommended for approval for the treatment of ocular itching associated with allergic conjunctivitis with the minor editorial revision listed below and indicated in the attached labeling:

1. In the Section 8 **USE IN SPECIFIC POPULATIONS**/8.1 Pregnancy, the title "DATA" should be added to the paragraph on animal data.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

NDA 208694 Zerviate (cetirizine ophthalmic solution) 0.24% is recommended for approval for the treatment of ocular itching associated with allergic conjunctivitis.

- Risk Benefit Assessment

The results from the two efficacy trials (Studies 12-100-0006 and 13-100-0002), demonstrate a statistically significant and marginally clinically significant difference between cetirizine ophthalmic solution, 0.24% and vehicle for the prevention of ocular itching associated with allergic conjunctivitis.

The most frequent ocular adverse reactions were ocular hyperemia (including conjunctival) (7%), and instillation site pain (4%). There were no non-ocular adverse reactions that occurred at a frequency of ≥ 1 %.

The benefits of using this drug product outweigh the risks for the treatment of ocular itching associated with allergic conjunctivitis.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

There are no recommended postmarketing risk evaluation and management strategies (i.e. REMS) for this drug product.

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- Recommendation for other Postmarketing Requirements and Commitments

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

- Recommended Comments to Applicant

None.

Appendix

NDA 208694 Zerviate (cetirizine ophthalmic solution) 0.24% is recommended for approval for the treatment of ocular itching associated with allergic conjunctivitis with the minor editorial revision listed below and indicated in the attached labeling submitted 5/1/17:

1. In the Section 8 **USE IN SPECIFIC POPULATIONS**/8.1 Pregnancy, the title "DATA" has been added to the paragraph on animal data.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

WILLIAM M BOYD
05/19/2017

WILEY A CHAMBERS
05/22/2017