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APPLICATION NUMBER:

208694Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208694
Supporting document/s:	SD 17 (original new NDA, resubmission/Class 2, submitted 3/08/2017)
Applicant's letter date:	March 8, 2017
CDER stamp date:	March 8, 2017
Product:	Cetirizine ophthalmic solution, 0.24% (Zerviate™)
Indication:	Treatment of ocular itching associated with allergic conjunctivitis
Applicant:	Nicox Ophthalmics, Inc. Fort Worth, Texas 76102
Review Division:	Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), CDER, HFD-590
Reviewer:	Andrew J. McDougal, PhD, DABT, DTOP
Supervisor/Team Leader:	Lori E. Kotch, PhD, DABT, DTOP
Division Director:	Renata Albrecht, MD, DTOP
Project Manager:	June Germain

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Except as specifically identified, Nicox Ophthalmics, Inc. claims ownership or right of reference to all data and information discussed below and necessary for approval of NDA 208694.
Any information or data necessary for approval of NDA 208694 that Nicox Ophthalmics, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Other data or information described or referenced below from reviews or publicly available summaries were not relied upon for approval of NDA 208694.

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1 Executive Summary

1.1 Introduction

- Pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, the Applicant (Nicox Ophthalmics, Inc.; Nicox) submitted original NDA 208,694 for Zerviate™ (Cetirizine Ophthalmic Solution, 0.24%) on April 18, 2016.
- 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 20346[1]; the findings of safety and efficacy are the same for both.
- P/T has recommendations regarding the Applicant's proposed labeling (please see below).
- The NDA was submitted electronically (available internally via: \\CDSESUB1\evsprod\NDA208694\208694.enx)

1.2 Brief Discussion of Nonclinical Findings

- Reference is made to the previous P/T review (McDougal, 9/17/2016, NDA 208694).
- No new nonclinical data were submitted in the 3/08/2017 Resubmission – Complete Response Amendment.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, DTOP recommends approval of this NDA 208694.

[1] Zytrec® (cetirizine hydrochloride) tablets and syrup for oral use. Pages 13-25 of the pdf file accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/19835slr016,21150slr005,30346slr011_zyrtec_lbl.pdf

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Reference is made to the previous P/T review (McDougal, 9/17/2016, NDA 208694), and to the Cross-Discipline Team Leader (CDTL) review (Boyd, 10/07/2016, NDA 208694).

The Applicant submitted annotated draft labeling in the 3/08/2017 NDA resubmission (\\cdsesub1\evsprod\nda208694\0017\m1\us\annotated-draft-labeling-text.pdf).

P/T is recommending changes for two sections (11 Description and 12.1 Mechanism of Action). Briefly:

- The Applicant has not provided data demonstrating that cetirizine is a [redacted] (b) (4) DTOP previously discussed this issue with the Applicant, who agreed to remove the language (e.g. Section 1 Indications and Usage, Section 12.1 Mechanism of Action) from the proposed labeling.
  - The use of the language in Section 11 was previously overlooked. P/T now recommends that [redacted] (b) (4) be removed from section 11.
  - This approach is consistent with the 2017 Labeling Review Tool (LRT), which advises for section 12.1, "MOA for indications or uses not included in the INDICATIONS AND USAGE section of the labeling must not be included in this subsection."[2]
- Section 12.1 Mechanism of Action begins with the statement, "ZERVIATE is a histamine-1 (H1) receptor antagonist (antihistamine)." The Applicant has proposed to append wording to this sentence: [redacted] (b) (4) P/T recommends not accepting this change.
  - The established pharmacological class (EPC) for cetirizine is "histamine-1 (H1) receptor antagonist"[3]. The labeling for NDA 020346 uses the word "antihistamine" as well.
  - This Applicant's proposed statement is scientifically correct, [redacted] (b) (4)
  - [redacted] (b) (4) .
  - In modulen 1.14.1.3 of the NDA (draft-labeling-text-tracked-changes, \\cdsesub1\evsprod\nda208694\0017\m1\us\draft-labeling-text-tracked-

[2] 2017 LRT accessed via: http://inside.fda.gov:9003/downloads/cder/officeofnewdrugs/immediateoffice/labelingdevelopmentteam/ucm541522.pdf

[3] FDA Established Pharmacologic Class (EPC) Text Phrase. Accessed via: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM428333.pdf

changes.docx), the Applicant provided a justification for the additional language, under section 12.1 of the labeling: "Section 2.7.3.1 of NDA; and supportive references (Section 5.4 (b) (4)

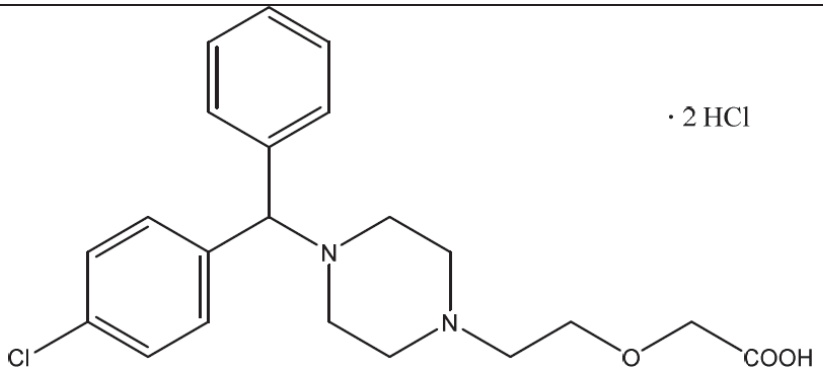
- The two papers mentioned were submitted in the original (4/18/2016) NDA, and were previously reviewed by P/T (McDougal, 9/17/2016, NDA 208694). (b) (4)

Previous P/T recommendations	Applicant's proposed language (4/18/2016)	P/T current recommendations
n/a	**11 DESCRIPTION** ZERVIATE is a sterile ophthalmic solution containing cetirizine, which is a histamine-1 (H1) receptor antagonist (b) (4) or topical administration to the eyes. …	**11 DESCRIPTION** ZERVIATE is a sterile ophthalmic solution containing cetirizine, which is a histamine-1 (H1) receptor antagonist (b) (4) for topical administration to the eyes.
12. Mechanism of Action ZERVIATE is an antihistamine; it is a histamine-1 (H1) receptor antagonist. Its principal effects are mediated via selective inhibition of peripheral H1 receptors. The antihistaminic activity of cetirizine has been clearly 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	**12.1 Mechanism of Action** ZERVIATE (b) (4) Its effects are mediated via selective inhibition of H1 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	**12.1 Mechanism of Action** ZERVIATE, **an antihistamine,** is a histamine-1 (H1) receptor antagonist (b) (4) Its effects are mediated via selective inhibition of H1 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

no measurable affinity for other than H1 receptors.	no measurable affinity for other than H1 receptors.	activity. In vitro receptor binding studies have shown no measurable affinity for other than H1 receptors.

2 Drug Information

2.1 Drug

CAS Registry Number	83881-52-1
Generic Name	Cetirizine Hydrochloride
Other Names	• Cetirizine • Cetirizine dihydrochloride • 1143 • AC170
Chemical Name	(RS)-2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride
Molecular Formula	$C_{21}H_{25}ClN_2O_3 \cdot 2HCl$
Molecular Weight	461.80
Structure	 **Figure 1: Structure of cetirizine hydrochloride**
Pharmacologic Class	H_1-receptor antagonist

Note: cetirizine has one stereocenter. The drug substance for this NDA is racemic (NDA module 2.3.S).

2.5 Comments on Impurities/Degradants

- Reference is made to the previous P/T review (McDougal 9/17/2016, NDA 208694), which concluded that "exposures to three identified leachables, as well as eight unidentified leachables, were not concerning."
- P/T was informed by the Product Quality Reviewer that two leachables were newly identified: (b) (4)
- P/T concludes that the exposures to (b) (4)

Table 1: Estimated exposures to two identified leachables from the bottle for cetirizine ophthalmic solution 0.24%

Exposure	Highest concentration detected (µg/ml)	Daily exposure per eye (µg/eye/day)[a]	Maximum daily exposure per person (µg/person/day)[b]
(b) (4)			

[a] Based on the labeling dosage and administration of "one drop in each affected eye twice daily", assuming a drop size of 37 µl (i.e. assuming 74 µl/day/eye). This assumption is conservative; (the Applicant reported that the actual drop size was 32.1 to 37.0 µl (NDA module 3.2.P.2, file 'drop-size-study-report-42-840.pdf').
[b] Assuming both eyes dosed twice daily, and assuming 100% systemic absorption.

Chemical name		(b) (4)
Safety summary:		
Chemistry information	CAS #	
	Other names/synonyms	

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(b) (4)

4 Pharmacology

- Cetirizine is an antihistamine drug. The current established pharmaceutical class (EPC) for cetirizine is "histamine-1 (H1) receptor antagonist".

(b) (4)

[20] Maintained by the National Institutes of Health, National Library of Medicine. https://toxnet.nlm.nih.gov/cpdb/

[21] NDA 20-688/SLR-016. Accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20688slr016_patanol_lbl.pdf

7 Genetic Toxicology

No genetic toxicology study reports were submitted to the NDA. The labeling for NDA 020346 for Zyrtec® (cetirizine hydrochloride) summarizes genetic toxicology data, and this NDA relies on the Agency's previous finding of safety for NDA 020346, as reflected in the drug's approved labeling.

8 Carcinogenicity

No carcinogenicity studies were submitted to the NDA. The labeling for NDA 020346for Zyrtec® (cetirizine hydrochloride) summarizes rodent carcinogenicity data, and this

[22] NDA 21-565/S-006. Accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021565s006lbl.pdf
[23] NDA 22-288/S-003. Accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022288s003lbl.pdf
[24] NDA 22-134/S004. Accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022134s004lbl.pdf

NDA relies on the Agency's previous finding of safety for NDA020346, as reflected in the drug's approved labeling.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No fertility or early embryonic development studies were submitted to the NDA. The labeling for NDA 020346 for Zyrtec® (cetirizine hydrochloride) summarizes nonclinical fertility data, and this NDA relies on the Agency's previous finding of safety for NDA020346, as reflected in the drug's approved labeling.

9.2 Embryonic Fetal Development

No embryofetal development (EFD) studies were submitted to the NDA. The labeling for NDA 020346 for Zyrtec® (cetirizine hydrochloride) summarizes EFD data, and this NDA relies on the Agency's previous finding of safety for NDA 020346, as reflected in the drug's approved labeling.

11 Integrated Summary and Safety Evaluation

- The Applicant provided nonclinical data to support the safety of topical ocular cetirizine, which were previously reviewed (McDougal, 9/17/2016, NDA 208694).
- 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.
- FDA approved a single prescribing label[25] in 2004 for both NDA 19835 and NDA 20346. Therefore, the findings of safety and efficacy are necessarily identical.

[25] For both NDAs, FDA has published the labeling at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/19835slr016,21150slr005,30346slr011_zyrtec_lbl.pdf

11.1 From oral cetirizine to ophthalmic cetirizine, the dose margin is 28.2 x

- Comparing the approved oral dose of Zyrtec (10 mg/person/day) to the proposed ophthalmic dose (up to 4 drops/person/day), the exposure margin is 28.15x
- For Zerviate™, the Applicant measured the drop volume; the range was 32.1 to 37.0 µl (NDA module 3.2.P.2, file 'drop-size-study-report-42-840.pdf'). This review will use 37.0 µl for the exposure margin calculations.
- Zerviate™ is 0.24% cetirizine (b) (4) The draft labeling dosage and administration of "one drop in each affected eye twice daily". Assuming both eyes are dosed with a total of two 37 µl drops per day, the daily dose
  - = 177.6 µg/eye/day of cetirizine
  - = **355.2 µg/person/day** of cetirizine.

  Assuming the patient body weight is 60 kg, and assuming[26] a k_M body surface area (BSA) conversion factor of 37,
  - = 5.92 µg/kg/day of cetirizine
  - = 219.04 µg/m^2/day of cetirizine
  - =0.21904 mg/m^2/day of cetirizine
- As the labeling for NDA 020346 notes, "The recommended initial dose of ZYRTEC is 5 or 10 mg per day in adults". Using the same assumptions (body weight and BSA)
  - = 10 mg/person/day of cetirizine
  - = 0.167 mg/kg/day of cetirizine
  - = 6.167 mg/m^2/day of cetirizine

.

Table 2: Dose margin: comparing oral cetirizine (Zyrtec®) and ophthalmic cetirizine (Zerviate™)

Daily dose of cetirizine from Zyrtec®	Daily dose of cetirizine from Zerviate™	Exposure margin based on administered dose
10 mg	(b) (4)	

[26] CDER 2005 Guidance for Industry. Estimating the maximum safe starting dose in initial clinical trial for therapeutics in adult healthy volunteers. Accessed via: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078932.pdf

11.2 The systemic exposure margin based on PK/TK

- As noted above (in section 11.3 of this review), the NDA 019835 labeling reports that 10 mg oral dose resulted in a clinical C_{max} of 311 ng/mL
- The rabbit single-dose ocular distribution study (report # 2307-001) administered cetirizine 0.24% OU, once (single-dose), twice (bid for one day), or bid for 7 days. The highest mean plasma concentration was 26.28 ng/g (equivalent to ng/ml). This measurement may not be a true C_{max} (i.e. the time points selected may have missed the true C_{max}).

- The short-term topical ocular studies (reports # AC17-0156, AC170-083, and AC170-0845) did not report TK results.

- The rabbit 6-month topical ocular toxicity study (report # AC170-157) reported TK results (**Error! Reference source not found.** and **Error! Reference source not found.** of this review, above). The study tested cetirizine 0.24% qd and tid; the high-dose (tid) was the NOAEL.

    - The highest mean C_{max} for qd dosing was 57.9 ng/ml.

    - The highest mean mean C_{max} for tid dosing was 67.2 ng/ml.

Table 3: Systemic exposure margin comparisons

Topical ocular OU doses with cetirizine 0.24%	Highest mean C_{max} (ng/ml) value	Exposure margin from the plasma C_{max} of 311 ng/ml for the 10 mg oral dose
Rabbit distribution study	26.28	11.834 x
6-month study, qd dosing	57.9	5.371 x
6-month study, tid dosing	67.2	4.628 x

Note: using the highest mean C_{max} may overestimate the true exposure; therefore these exposure margins are considered protective.

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/s/

ANDREW J MCDOUGAL
05/11/2017

LORI E KOTCH
05/11/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208694
Supporting document/s:	SD 1 (original new NDA, submitted 4/18/2016)
Applicant's letter date:	April 18, 2016
CDER stamp date:	April 18, 2016
Product:	Cetirizine ophthalmic solution, 0.24% (Zerviate™)
Indication:	Treatment of ocular itching associated with allergic conjunctivitis
Applicant:	Nicox Ophthalmics, Inc. Fort Worth, Texas 76102
Review Division:	Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), CDER, HFD-590
Reviewer:	Andrew J. McDougal, PhD, DABT, DTOP
Supervisor/Team Leader:	Lori E. Kotch, PhD, DABT, DTOP
Division Director:	Renata Albrecht, MD, DTOP
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1 Executive Summary

1.1 Introduction

- Pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, the Applicant (Nicox Ophthalmics, Inc.; Nicox) submitted original NDA 208,694 for Zerviate™ (Cetirizine Ophthalmic Solution, 0.24%) on April 18, 2016.
    - The proposed indication is the treatment of ocular itching associated with allergic conjunctivitis.
    - The proposed dosing regimen is 1 drop in each affected eye twice daily.
    - Zerviate™ is a new dosage form, and will be supplied as a preserved ophthalmic solution in multi-dose bottles.
- Studies in support of this NDA were conducted under IND (b) (4) and IND 108558 (for which Nicox is the Sponsor). The NDA's nonclinical package includes an ocular distribution study and topical ocular toxicology studies.
- This NDA was filed under the 505(b)(2) pathway, listing NDA 019835 for Zyrtec® (cetirizine hydrochloride) tablets.
- The NDA was submitted electronically (available internally via: \\CDSESUB1\evsprod\NDA208694\208694.enx)

1.2 Brief Discussion of Nonclinical Findings

- From a nonclinical Pharmacology/Toxicology (P/T) perspective, topical ocular dosing with cetirizine ophthalmic solution, 0.24% was well-tolerated.
    - The nonclinical studies associated topical cetirizine ophthalmic solution, 0.24% treatment with hyperemia. This finding was subsequently observed 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, increased 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.

- This P/T review has 4 areas of focus:
    - Reviewing the safety of potential exposure to three identified leachables. These exposures are not concerning from a regulatory perspective.
    - Reviewing the Applicant's proposed changes to the mechanism of action labeling for cetirizine. P/T does not concur with the Applicant's proposal to add the term (b) (4) to section 12.1 of labeling.

- Reviewing the five nonclinical study reports for topical ocular cetirizine (tested alone or as a combination). Topical ocular cetirizine was well tolerated, and no new safety concerns were identified.
- Verifying the Applicant's exposure margin estimates for Section 8.1 and Section 13 of labeling. This reviewer does not concur with the Applicant's calculations.

505(b)(2) considerations

- For NDAs submitted under the under the 505(b)(2) pathway, CDER's Office of New Drugs (OND) has requested that P/T verify whether the NDA provides an adequate bridge to the listed drug(s) and whether reliance is scientifically appropriate.
- The Applicant states (in the April 18, 2016 cover letter), that in addition to Nicox's own data, the NDA "also relies, in part, on the Agency's previous findings of safety for the reference listed drug, Zyrtec® (cetirizine hydrochloride) Tablets (NDA 019835). Nicox believes that such reliance is scientifically appropriate based upon comparative bioavailability." From a P/T perspective, this reviewer concurs.
- The active ingredient in Zerviate™ is cetirizine, the same active ingredient in Zyrtec®.
  - This NDA is not for a new chemical entity (NCE) or new molecular entity (NME).
  - Zerviate™ differs from Zyrtec® in the formulation, and the route of administration (topical ocular for Zerviate™; oral for Zyrtec®).
- 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 described in Clinical Pharmacology section of the Zyrtec® labeling). P/T defers to Clinical Pharmacology, regarding the comparison of the clinical PK data for Zerviate™ with the clinical PK data for Zyrtec®.
- Although cetirizine is marketed in the U.S. over-the-counter (OTC), no OTC monograph has not yet been published for cetirizine.
- The Applicant is not relying on publications to support the nonclinical package. The Applicant provided several published papers (NDA module 4.3 Nonclinical Literature References) for completeness.
  - Review of these papers did not identify new information that affected the safety evaluation of Zerviate™, or that would warrant changes to labeling.
  - Review of these papers did not find any trade names for cetirizine other than the trade name of the listed product (Zyrtec®), or any source other than the source of the listed product (i.e. manufactured and marketed by Pfizer, and marketed by UCB).

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, DTOP recommends approval of this NDA 208694.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

- The Applicant submitted annotated draft labeling in the original NDA submission (\\cdsesub1\evsprod\nda208694\0001\m1\us\annotated-draft-labeling-text.pdf).
- The exposure margin calculations are detailed in section 11.6 of this review (below). Essentially, the Applicant proposed exposure margins based on dose (mg/kg), presuming single eye dosing. P/T recommends calculating the exposure margins based on body surface area (BSA) scaling, presuming dosing of both eyes (OU).

Listed drug labeling (2004) for NDA 019835	Applicant's proposed language (4/18/2016)	P/T recommendations
n/a	**1. INDICATIONS AND USAGE** TRADENAME® is indicated for treatment of ocular itching associated with allergic conjunctivitis.	**1. INDICATIONS AND USAGE** Zerviate™ is a histamine-1 (H1) receptor antagonist indicated for treatment of ocular itching associated with allergic conjunctivitis.
	8.1. Pregnancy *Risk Summary* There were no adequate or well-controlled studies with TRADENAME® in pregnant women. Cetirizine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.	**8.1. Pregnancy** *Risk Summary* [P/T defers to Clinical]
Pregnancy Category B: In mice, rats, and rabbits, cetirizine was	*Animal Data* Cetirizine was not teratogenic in mice, rats, and rabbits at	*Animal Data* Cetirizine was not teratogenic in mice, rats, **or** rabbits at oral

not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180 and 220 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.	oral doses up to 96, 225, and 135 mg/kg, respectively (b) (4) times the maximum recommended human ophthalmic dose (MRHOD)).	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* (b) (4) (b) (4) 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 (C_{max} = 311 ng/mL) that were (b) (4) times higher than the	**8.2. Lactation** Risk Summary Cetirizine has been reported to be excreted in human breast milk following oral administration. Administration of cetirizine ophthalmic solution 0.24% at RHOD produced systemic levels that were approximately 10% of those observed following multiple doses of oral cetirizine administration (10mg tablet) *[see section 12.3].* It is not known whether measurable levels of cetirizine would be present in maternal milk following topical ocular administration. There is no adequate information regarding the effects of cetirizine on

	observed human exposure (C_{max} = 3.1 ng/mL) following twice-daily administration of cetirizine ophthalmic solution 0.24% to both eyes for one week. It is not known whether topical ocular administration could (b) (4) (b) (4) produce detectable quantities in human breast milk. (b) (4)	breastfed infants, or the effects on milk production to inform risk of TRADENAME® to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME® and any potential adverse effects on the breastfed child from TRADENAME® or from the underlying maternal conditions. *[P/T defers to Clinical Pharmacology and Clinical teams to assess adequacy of the proposed exposure margin, and whether any published patient lactation data (following oral cetirizine use) are appropriate for inclusion in labeling], respectively.*
Nursing Mothers: In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). Studies in beagle dogs indicated that approximately 3% of the dose was excreted in milk.	(b) (4)	

Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.		
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 25 times the maximum recommended daily oral dose in adults on a mg/m^2 basis).	(b) (4)	[P/T recommends deleting section 8.3, and moving the pertinent wording to section 13.1]
Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and ex *vivo animal models* have shown negligible	(b) (4)	**12. Mechanism of Action** ZERVIATE is an antihistamine; **it is a histamine-1 (H1) receptor antagonist**. Its principal effects are mediated via selective inhibition of peripheral H1 receptors**. The antihistaminic activity of cetirizine has been clearly 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**

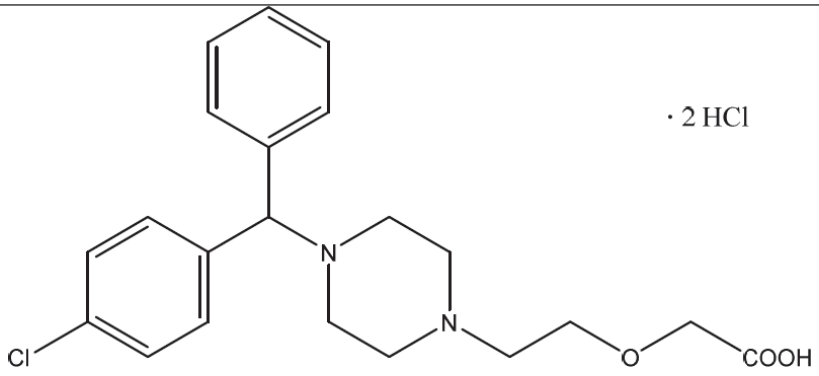
anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H1 receptors.		**binding studies have shown no measurable affinity for other than H1 receptors.**
Carcinogenesis, Mutagenesis and Impairment of Fertility: In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the	**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 3,100 times the MRHOD). In a 2-year	**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**).

maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 7 times the maximum recommended daily oral dose in infants 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 6 times the maximum recommended daily oral dose in adults on a mg/m2 basis, or approximately 3 times the maximum recommended daily oral dose in infants on a mg/m2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately equivalent to the maximum recommended	carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (b) (4) No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (b) (4) he clinical significance of these findings during long-term use of cetirizine are not known.	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 are not known.

daily oral dose in infants on a mg/m^2 basis). The clinical significance of these findings during long-term use of ZYRTEC is not known.		
Cetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and *in vivo* micronucleus test in rats.	*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.	[no change; P/T concurs with the Applicant's language]
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 25 times the maximum recommended daily oral dose in adults on a mg/m^2 basis).		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**).

2 Drug Information

2.1 Drug

CAS Registry Number	83881-52-1
Generic Name	Cetirizine Hydrochloride
Other Names	• Cetirizine • Cetirizine dihydrochloride • 1143 • AC170
Chemical Name	(RS)-2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride
Molecular Formula	$C_{21}H_{25}ClN_2O_3 \cdot 2HCl$
Molecular Weight	461.80
Structure	 **Figure 1: Structure of cetirizine hydrochloride**
Pharmacologic Class	H_1-receptor antagonist

Note: cetirizine has one stereocenter. The drug substance for this NDA is racemic (NDA module 2.3.S).

2.2 Relevant INDs, NDAs, and DMFs

NDA 019835	• The Applicant identified NDA 019835 Zyrtec (cetirizine hydrochloride) tablets as the listed drug being relied upon, as listed on form 356h. • The Applicant claims no right-of-reference to the confidential business information in NDA 019835.

	• Note: Johnson & Johnson Consumer Inc. is the application holder for NDA 0193835.
IND 108558	• Nicox Ophthalmics, Inc. is the current sponsor for IND 108558, as well as the Applicant for NDA 208694 (the subject of this review), and Nicox claims right of reference (NDA module 1.4.2). • The subject of the IND is cetirizine ophthalmic solution, 0.24% • This IND was originally submitted on 4/12/2010 by Aciex Therapeutics, Inc. Sponsorship was formally changed on February 25, 2016. The IND reports that Aciex Therapuetics is a wholly owned subsidiary of Nicox S.A. (e.g. the 2015 Annual Report, page 1). • Submissions to IND are internally available electronically, beginning 7/2014 (\\cdsesub4\NONECTD\IND108558)
[redacted] (b) (4)	
Other DMFs	• The NDA also has letters of authorization for DMF (b) (4), DMF (b) (4) DMF (b) (4), DMF (b) (4), DFM (b) (4), and DMF (b) (4). • Review of these DMFs is beyond the scope of this review.

2.3 Drug Formulation

- The Applicant reported (NDA module 3.2.P.1 Components of the Drug Product and module 3.2.P.2.2 Drug Product) that the formulation for cetirizine ophthalmic solution 0.24% has not changed (i.e. the nonclinical studies used the same formulation as was tested clinically, and as will be marketed).

Table 1: formulation of Cetirizine Ophthalmic Solution 0.24%

Component	mg/ml
Cetirizine	2.4
Benzalkonium chloride	(b) (4)
Sodium phosphate, dibasic, (b) (4)	
Edetate disodium, (b) (4)	
Polyethylene glycol 400	
Polysorbate 80	
Hypromellose (b) (4)	
Glycerin	
Water	

- Under IND 108558, the initial investigational drug product was initially (b) (4) (b) (4)

(b) (4)

- Note: review did not identify the formulation used for the rabbit study # P10800 (AC170-083) in the report or elsewhere in the NDA. The results of this study were not concerning, and this study was not pivotal to the safety assessment of cetirizine.

2.4 Comments on Novel Excipients

The cetirizine ophthalmic solution, 0.24% drug product has no novel excipients. Each excipient has been previously qualified for topical ocular administration.

2.5 Comments on Impurities/Degradants of Concern

During the review, this reviewer confirmed for the Office of Product Quality (OPQ) reviewer (personal communication, McDougal/Feng, 8/23/2016) that exposures to three identified leachables, as wells as eight unidentified leachable compounds, were not concerning.

The Applicant reported (NDA module 3.2.P.2.4 Container Closure System)[1] that three possible leachables had been identified, based on a report titled "Leachables Report for [redacted] (b) (4)

Table 3: Estimated exposures to leachables from the bottle for cetirizine ophthalmic solution 0.24%

Exposure	Highest concentration detected, or lower limit of detection (µg/ml)[a]	Daily exposure per eye (µg/eye)[b]	Daily exposure per person (µg/person)[c]
[redacted] (b) (4)			

[1] Accessed internally from the EDR via: \\cdsesub1\evsprod\nda208694\0001\m3\32-body-data\32p-drug-prod\cetirizine-ophthalmic-solution-ophthalmic-drops\32p2-pharm-dev\container-closure-system.pdf

[2] Accessed internally from the EDR via: \\cdsesub1\evsprod\nda208694\0001\m3\32-body-data\32p-drug-prod\cetirizine-ophthalmic-solution-ophthalmic-drops\32p2-pharm-dev\contain-closure-sys-test-rpt-prot-42-906.pdf

[a] For (b) (4), and unidentified leachables, the highest concentrations are shown. (b) (4) was not detected, and the table shows the lower limit of detection (LLOD).
[b] Based on the labeling dosage and administration of "one drop in each affected eye twice daily", assuming a drop size of 37 µl (i.e. assuming 74 µl/day/eye). This assumption is conservative; (the Applicant reported that the actual drop size was 32.1 to 37.0 µl (NDA module 3.2.P.2, file 'drop-size-study-report-42-840.pdf').
[c] Assuming both eyes dosed twice daily, and assuming 100% systemic absorption.

Although (b) (4) are both photoinitiators (and therefore presumed to be potentially genotoxic following topical ocular exposure), the available data and exposure estimates, considered together, provide a weight-of-evidence for the lack of regulatory concern.

Safety data summary for the three identified leachables

(b) (4)

	Safety summary	• The Applicant's Leachables Report cites a 2011 (b) (4) material safety data sheet (MSDS; not provided to the NDA); this reviewer identified several MSDS sheets online, which did not have toxicology experimental results • (b) (4) reports commercial use (b) (4)

		• Relevant toxicology data was obtained from the [(b) (4)] database[4]: o Genotoxicity *in vitro* data: ▪ negative Ames test ▪ negative in HRPT test in Chinese Hamster Ovary cells o GLP 90-day oral rat toxicology study: ▪ NOAEL of 50 mg/kg/day o Liver effects at 400 mg/kg: increased cholesterol, increased liver weight, centrilobular hypertrophy o Kidney effects at 400 mg/kg: urinalysis changes (sediment, crystals, pH ↓, specific gravity ↑), kidney weight increase, renal granular casts and basophilic tubules. o Rabbit eye irritation study: ▪ Non-GLP study conducted in 1980, following OECF 405 (acute eye irritation/corrosion) ▪ 100 µl dose was slightly irritating (cornea opacity, iris irritation, conjunctivae erythema and secretion) with recovery by D4. • Other data (results are not concerning for this exposure level): o Rat lethality (LD_{50}) data[5] o Results of a secondary pharmacology screen[6]
	Risk character-ization for [(b) (4)]	• Because the route of exposure for the drug product is topical ocular dosing, the photoinitiating properties of [(b) (4)] are presumed to be relevant. Therefore, theoretical concern is that [(b) (4)] will be mutagenic and carcinogenic following topical ocular exposure. • The negative *in vitro* genotoxicity test results mitigate

[(b) (4)]

		this theoretical concern. • The lack of moderate (or worse) irritation in the rabbit eye study (summarized by (b) (4)) mitigates the concern that (b) (4) may have potent activity (as a mutagen or carcinogen) • The ICH M7 guideline[7] considers (b) (4) µg/person/day (systemic exposure) to be an acceptable intake of a mutagenic impurity. This is a useful benchmark for considering the potential acceptability of topical ocular exposures. • For the drug product, the labeling dosage and administration has no limitation on the duration of use for the drug product (e.g. ICH M7 guidelines regarding the short-term durations of exposure are not relevant) • (b) (4) was "below the limit of detection" ((b) (4) µg/ml) for 23 samples, and was detected ((b) (4) µg/ml) in 3 samples. Therefore the risk estimate in the table above is considered unlikely to underestimate risk.
	Safety conclusion for (b) (4)	Based on the highest estimated exposure of (b) (4) µg/person/day, and the ICH M7 benchmark of (b) (4) µg/person/day, this reviewer does not consider the potential exposure from (b) (4) to be concerning.
(b) (4)		

	weight	
	Molecular formula	(b) (4)
	Safety data	• The Applicant cites a 2010 MSDS from (b) (4) and reports that (b) (4) is non-toxic following oral and dermal dosing. • No genotoxicity data identified by the Applicant or this reviewer.
		A literature search found: • That (b) (4) is marketed as a photoinitiator[9] [this same document also lists (b) (4) as another photoinitiator]. • A report[10] that (b) (4) exposure (b) (4) is common, and that "no studies on health effects [are] available". It is not clear how significant this exposure to (b) (4) is, compared to other exposures.
	Risk Character-ization	• Because (b) (4) is reportedly a photoinitator, a theoretical concern is that it has (b) (4) will be mutagenic and carcinogenic following topical ocular exposure (i.e. the same theoretical concern as for (b) (4), reviewed above). • (b) (4) was found in all batches tested.
	Safety conclusion for (b) (4)	Based on the highest estimated exposure of (b) (4) µg/person/day, and the ICH M7 benchmark of (b) (4) µg/person/day, this reviewer does not consider the potential exposure from (b) (4) to be concerning.
(b) (4)		

(b) (4)		
	Safety notes	• (b) (4) is reportedly (b) (4) (b) (4) and has been investigated for potential angiogenic activity. • (b) (4) is listed as an (b) (4) without a specified limit. • The Applicant reports that (b) (4) was "not detected in any batch at any time point as a leachable". The limit of detection = (b) (4) µg/ml. • This reviewer concludes that the potential exposure to
(b) (4)		

		(b) (4)
Unidentified leachable	Exposure and safety notes	• The levels detected varied; the highest estimated exposure is (b) (4) µg/person/day. • This reviewer concludes that these exposures are not concerning, and concurs with the Chemistry reviewer that identification of individual impurities is not warranted for this particular dosage and route of administration.

2.6 Proposed Clinical Population and Dosing Regimen

- Proposed clinical population:
  - The Applicant's proposed indication is "treatment of ocular itching associated with allergic conjunctivitis."
  - Language in the Applicant's proposed labeling refers to clinical trials conducted for "patients with allergic conjunctivitis or those at a risk of developing allergic conjunctivitis."
  - The Applicant's proposed labeling reports "The safety and effectiveness of ZERVIATE has been established in pediatric patients two years of age and older." and "No overall differences in safety or effectiveness have been observed between elderly and younger patients."
- Proposed dosing regimen: "one drop in each affected eye twice daily."
  - Because the drug product is 0.24% cetirizine, this daily dose corresponds to 178 µg/eye/day (assuming a 37 µl drop size).

2.7 Regulatory Background

- IND 108558 for cetirizine was submitted to DTOP in April 2010.
- A pre-NDA meeting was held, under IND 108558, on December 16, 2014 between DTOP and the IND Sponsor.
  - The IND Sponsor, Aciex Therapeutics, is wholly owned by Nicox, the NDA Applicant.
  - Sponsorship of the IND formally transferred from Aciex to Nicox in March 2016.
- The Applicant submitted the original NDA 208694 on April 18, 2016.
- No P/T information request has been conveyed to the Applicant during the NDA review.

3 Studies Submitted

3.1 Studies Reviewed

Applicant's study #	Study # on report cover	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

3.2 Studies Not Reviewed

All nonclinical studies submitted to the NDA have been reviewed. The Applicant also submitted 16 nonclinical literature references (NDA module 4.3) for completeness. These were considered, but reviews of these references are not fully documented in this review, since the information contained within was not essential for approval.

3.3 Previous Reviews Referenced

This review of NDA 208694 references the previous reviews available in the CDER Document Archiving, Reporting and Regulatory Tracking System (DARRTS) for:

- IND 108558 nonclinical reviews: Wild 9/21/2010, Kotch 4/19/2012, McDougal 12/08/2014, McDougal 12/09/2014 [each of these reviews is in DARRTS].
- (b) (4)

4 Pharmacology

- The Applicant did not submit primary pharmacology, secondary pharmacology, or safety pharmacology studies to the NDA. This NDA is submitted under the 505(b)(2) pathway, relying on the Agency's finding of safety for NDA 019835 for

Zyrtec® (cetirizine hydrochloride) tablets to address these nonclinical topics. This approach is acceptable.

(b) (4)

- This reviewer recommends that the proposed change be rejected:
  - The NDA does not provide adequate support for this change.

[16] The FDA EPC Text Phrases for Indications and Usage heading in Highlights. August 2016. Accessed via http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM428333.pdf and http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

[17] NIH's US National Library of Medicine. Class Browser. Established Pharmacological Classes (EPC). Accessed via: https://mor.nlm.nih.gov/RxClass/

7 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

5 Pharmacokinetics/ADME/Toxicokinetics

- The Applicant submitted one ocular distribution study to support the NDA.
- This NDA is submitted under the 505(b)(2) pathway, relying on the Agency's finding of safety for NDA 019835 for Zyrtec® (cetirizine hydrochloride) tablets to address systemic absorption, distribution, metabolism, and elimination (ADME). This approach is acceptable.

Study title: Ocular tissue distribution and melanin binding of [14C]cetirizine in male rabbits following ocular administration

Study no.:	2307-001
Study report location:	NDA module 4.2.2.3 Nonclinical Study Reports – Pharmacokinetics – Distribution (\\cdsesub1\evsprod\nda208694\0001\m4\42-stud-rep\422-pk\4223-distrib\report-2307-001\report-body.pdf)
Conducting laboratory and location:	(b) (4)
Report date:	October 17, 2014
Date of study initiation:	June 6, 2014
GLP compliance:	Yes, signed • The authors noted the lack of stability information for the test article as a GLP deviation. • The report lacks information regarding the vehicle formulation, and this is a study limitation.
QA statement:	Yes, signed
Drug, lot #, and % purity:	[carbonyl-^{14}C]cetirizine HCl salt • Lot # 91-060-0589-A-20140619-DLE • Purity: 97.8% • Specific activity: 58.9 mCi/mmol

Key Study Findings

- Topical ocular dosing with cetirizine resulted in low but detectable levels in the plasma (~10-fold lower than the plasma levels reported in labeling for the listed drug, Zyrtec®, following oral dosing).
- Topical ocular dosing also resulted in low but detectable exposure of the retina.
- Following a single topical ocular dose, radiolabeled cetirizine distributed: cornea > eyelids > conjunctiva > iris/ciliary body > nictitating membrane > sclera > aqueous humor > retina/choroid > lacrimal gland (w/ harderian gland) > optic nerve > lens > vitreous humor > plasma

- Elimination was via urine (21%) and feces (12%). [These numbers suggest that systemic absorption was ~33%, and therefore suggest that the remainder may have spilled out of the eye]
- Melanin binding was not reported
    - The main ocular tissue distribution study was conducted in Dutch Belted (DB) rabbits.
    - Two additional groups of New Zealand White (NZW) rabbits were used, with a limited tissue panel (plasma, retina, choroid) to assess melanin binding.

Methods	
Doses:	0.24% cetirizine ophthalmic solution
Frequency of dosing:	• Single dose • Two doses (administered 8 hours apart) total • BID (two daily doses, 8 hours apart) for 7 days
Route of administration:	Topical ocular OU • "following dosing, dry gauze was used to wipe the external part of the eye", and then • A separate pieced of "gauze wettened with water was used to wipe the external part of the eye to remove any unabsorbed" dose • Both wipes/eye were collected and analyzed by liquid scintillation counting to determine the 'actual' administered dose (i.e. the amount on the wipes was subtracted from the total dose administered)
Dose volume:	• 40 µl nominal • Actual volumes were determined after each dose, by weighing the dosing syringe before and after dosing
Formulation/Vehicle:	• Not specified in the study report (see section 2.3 of this review, above) • Vehicle batch # PD12-003, used as supplied
Species/Strain:	Male Dutch Belted (DB) rabbits and male New Zealand White (NZW) rabbits
Number/Sex/Group:	3 to 18 males/group
Age:	• DB rabbits: 6 to 7.5 months at time of dosing • NZW rabbits: 8.5 months at time of dosing
Weight:	• DB rabbits: 1.57 to 2.00 kg • NZW rabbits: 3.08 to 3.89 kg

Table 4: Dosing details for the rabbit ocular distribution study (report # 2307-001)

Group	Number of	# of doses	Target	Average	Actual	Actual

#	male rabbits, strain		treatment (µCi/rabbit] per dose	dose (mg of cetirizine) per rabbit	average dose (µCi/rabbit]	average dose (µCi/ kg body weigh]
1	15 DB	1 total	29.04	0.116	17.4733	9.6
2	18 DB	2 total	58.08	0.129	19.4048	10.8
3	3 DB	14 (BID for 7 days)	58.08	0.130	19.5398	10.6
4	6 NZW	2 total	58.08	0.154	23.1648	6.6
5	3 NZW	14 (BID for 7 days)	58.08	0.155	23.2960	6.7

Data in this table provided by the authors

Formulation Analysis

- The authors report (page 12) that the study Sponsor did not provide information regarding the vehicle's formulation, strength, purity, composition, stability, or other pertinent information.
- The radiolabeled [^{14}C]cetirizine hydrochloride salt was provided as a salt, and formulated in vehicle (with sodium hydroxide added). The target pH was not identified in the study report, and this is a minor study limitation.
- Formulation analysis was conducted prior to dosing and after dosing on D1, and after dosing on D7. The results were acceptable (no apparent degradation or change in concentration).

Safety Observations and Results

- Safety endpoints were twice-daily observations for morbidity, mortality, injury, and availability of food and water.
- No remarkable observations were made.

Ocular Distribution Endpoints and Results

- Terminal tissues were 3 rabbits/group/ time point
- Tissues collected for the DB rabbits were: plasma, conjunctiva, eyelids, cornea, iris/ciliary body (ICB), sclera, lens, optic nerve, retina/choroid, vitreous humor, aqueous humor, nictitating membrane, and lacrimal gland (with accessory Harderian gland attached).
- Tissues collected for the NZW rabbits were plasma, retina, and choroid only
- Note: review of the report did not identify the lower limit of detection (LLOD)

Table 5: Tissue collection time points for the rabbit ocular distribution study (report # 2307-001)

Group	Number of	# of doses	Tissue collection time points

#	male rabbits, strain		
1	15 DB	1 total	Post dose at 0.5, 1, 2, 4, and 8 hours
2	18 DB	2 total	After the first dose at 8.5, 9, 10, 12, 16 and 24 hours
3	3 DB	14 (BID for 7 days)	1 hour after the final dose [urine and feces were also collected]
4	6 NZW	2 total	1 and 4 hours after the final dose
5	3 NZW	14 (BID for 7 days)	1 hour after the final dose

- The authors provided summary graphs, but not concise summary tables. This reviewer compiled the following tables from the report results (pages 72-82). The graphs are copied from the study report (pages 24-29).
- Recovery of radioactivity from feces and urine was assayed for group 3 only. The authors concluded, "Elimination of [14C] cetirizine derived radioactivity was predominantly in the urine, with mean totals of 20.58 ± 6.63% and 12.09 ± 0.46% recovered in urine and feces through 153 hours post dose, respectively."

Table 6: Cetirizine ocular distribution results for group 1: male Dutch Belted (DB) rabbits, single topical ocular OU dose with radiolabeled 0.24% cetirizine (report # 2307-001)

Group 1 data (DB rabbits, single topical ocular OU dose)					
Tissue	Mean concentration (ng-equivalent/g) at each post-dose time point				
	30 minutes	1 hr	2 hr	4 hr	8 hr
Plasma	26.98	14.59	8.24	0.98	BLLOD
Aqueous humor	205.42	333.77	300.17	111.06	23.65
Conjunctiva	1420.01	1372.77	982.70	969.19	364.21
Cornea	4666.58	3145.27	2912.72	931.93	259.55
Eyelids	2951.18	1226.43	1809.83	1724.48	869.61
Iris/ciliary body	372.59	902.27	761.80	333.88	125.76
Lacrimal/ Harderian	54.52	72.67	32.27	21.55	10.88
Lens	2.86	7.11	7.09	5.86	7.08
Nictitating membrane	850.84	442.42	485.74	320.12	270.73
Optic nerve	35.76	32.45	33.23	13.67	27.84
Retina / choroid	296.97	255.95	207.26	123.30	53.06
Sclera	601.54	225.53	227.37	91.35	59.76
Vitreous humor	4.09	7.60	5.50	2.42	2.85

BLLOD: below lower limits of detection

Figure 5: Cetirizine ocular distribution results for group 1 rabbits (C_{max} after a single OU dose) (report # 2307-001)

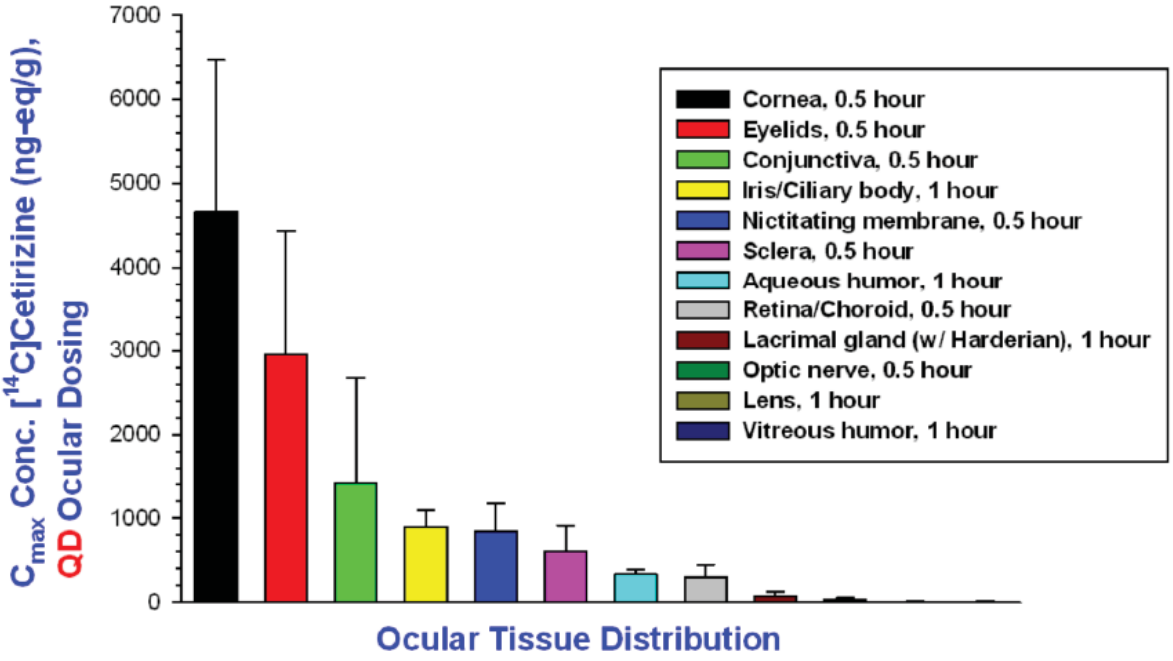


Table 7: Cetirizine ocular distribution results for group 2: male DB rabbits, two topical ocular doses OU with radiolabeled 0.24% cetirizine (report # 2307-001)

Group 2 data (DB rabbits, two single topical ocular OU doses (given 8 hours apart)						
Tissue	Mean concentration (ng-equivalent/g) at each time point (presented as time after the first dose)					
	8.5 hrs	9 hrs	10 hrs	12 hrs	16 hrs	24 hrs
Plasma	26.28	20.07	12.71	6.73	2.46	BLLOD
Aqueous humor	280.57	341.61	275.87	105.08	21.16	3.32
Conjunctiva	1995.63	295046	876.10	1625.52	852.07	1119.99
Cornea	5449.45	3813.62	1930.16	1141.92	518.06	248.84
Eyelids	2771.74	3461.92	1989.37	3700.94	4732.21	2906.61
Iris/ciliary body	646.95	926.62	706.19	282.32	156.51	46.61
Lacrimal/ Harderian	80.35	59.29	69.13	50.10	45.45	33.04
Lens	14.44	13.99	17.22	13.23	13.57	13.66
Nictitating	896.19	720.99	491.26	692.31	545.62	438.43

membrane						
Optic nerve	59.42	84.45	239.28	57.83	45.32	46.63
Retina / choroid	230.24	276.95	255.34	129.08	63.92	50.93
Sclera	538.75	327.25	200.46	204.35	121.94	133.11
Vitreous humor	4.97	5.08	5.88	3.32	3.22	2.91

BLLOD: below lower limits of detection

Figure 6: Cetirizine ocular distribution results for Group 2 rabbits (C_{max} after two OU doses) (report # 2307-001)

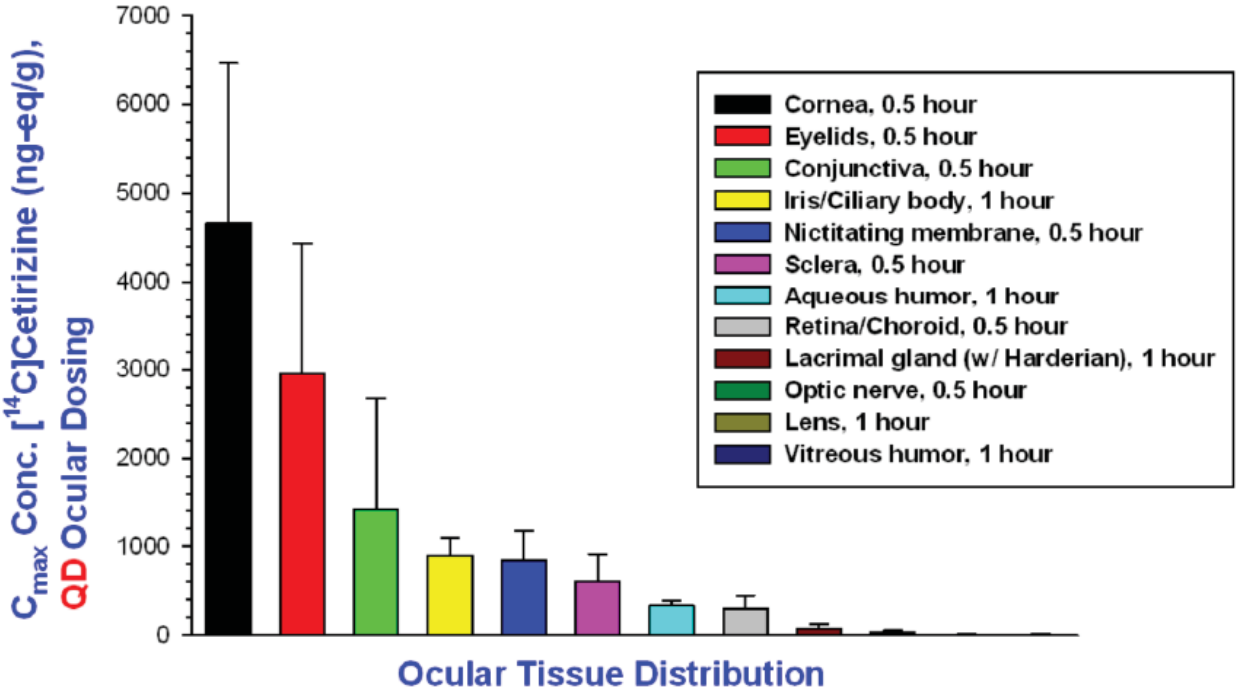
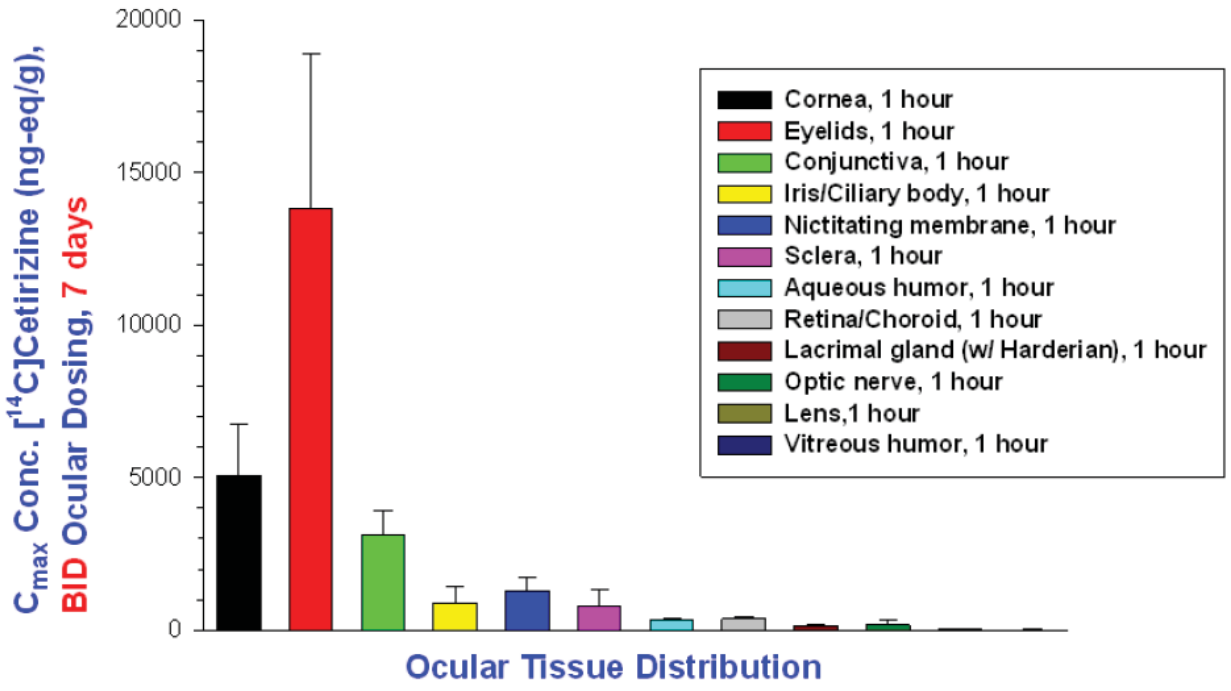


Table 8: Cetirizine ocular distribution results for group 3: male DB rabbits, BID topical ocular doses OU for 7 days with radiolabeled 0.24% cetirizine (report # 2307-001)

Group 3 data (DB rabbits, BID for 7 days OU (doses given 8 hours apart)	
Tissue	Mean concentration (ng-equivalent/g) at 1 hour after the last dose
	1 hr post-dose
Plasma	18.04
Aqueous humor	308.82

Conjunctiva	3107.56
Cornea	5076.98
Eyelids	13,823.15
Iris/ciliary body	875.92
Lacrimal/ Harderian	129.56
Lens	35.72
Nictitating membrane	1283.19
Optic nerve	164.31
Retina / choroid	370.73
Sclera	762.61
Vitreous humor	15.23

Figure 7: Cetirizine ocular distribution results for Group 3 rabbits (concentrations measured 1 hr after the last dose, OU BID for 7 days) (report # 2307-001)



*NOTE: This was a single group of animals euthanized 1 hour post 7 days of BID dosing (total cummulative time was 153 hours post start of dosing).

Table 9: Cetirizine ocular distribution data for groups 4 & 5: male NZW rabbits, dosed BID for 1 day (group 4) or 7 days (group 5) with radiolabeled 0.24% cetirizine (report # 2307-001)

Tissue	Mean concentration (ng-equivalent/g)		
	Group 4 (time points based on the first dose)		Group 5
	9 hrs	12 hrs	1 hour after the last dose
Plasma	8.38	3.87	21.12
Retina/choroid	183.34	69.91	444.52

Note: the authors did not measure the iris/ciliary body concentrations for the NZW rabbits; these data would have made the assessment of potential melanin-binding more robust.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were done to support this NDA. The Applicant relies upon the labeling for the listed drug, and noted that nonclinical oral acute lethality data were presented in labeling, under Overdosage. This reviewer does not consider these data to be relevant to Zerviate™, because the oral acute exposure levels cannot be reached by topical ocular dosing.

6.2 Repeat-Dose Toxicity

6.2.1 Repeat-Dose Toxicity

Study title:	**Five-day ocular tolerability study of cetirizine hydrochloride ophthalmic solution in rabbits**	
Study numbers:	• Study laboratory #: (b) (4) 2-5017-O-TX • Applicant's study #: AC170-156	
Key findings:	• Cetirizine hydrochloride 0.24% (QD or TID) was well-tolerated. o Slight white crusting at the corner of the eye was observed with the vehicle and test articles following topical ocular dosing. o Cetirizine 0.24% (QD or TID) was associated with an increased incidence of slightly red conjunctiva, and increased blinking. • This was a short-duration non-GLP ocular tolerability study (no necropsy of test animals).	
Report details	GLP status	Not GLP

	Study laboratory	(b) (4)
	Report date	August 24, 2012
	Date of study initiation	April 10, 2012
	Placebo:	• Lot # 1490563 • Contained edetate disodium dehydrate and benzalkonium chloride (amounts not reported) • pH 7.3
	Test articles:	0.024% cetirizine ophthalmic solution • Lot # 1490564 o Provided to the laboratory by (b) (4) o [Note: NDA module 2.3.P Drug Product Quality Overall Summary reports that this batch was manufactured 2/16/2011 by (b) (4), and was used in clinical trials # 11-100-012, 11-100-0013, and 11-100-0004] o Purity 95.2% o pH 7.1 o Osmolarity: 302 mOsm/kg • Certificates of analysis were provided by (b) (4) (i.e. not by (b) (4) the analytical laboratory for the clinical batch certificates of analysis) o Analysis detected edetate disodium dehydrate and benzalkonium chloride. The amounts were not reported (the certificate of analysis provides the results as a percentage of the specification, but did not report the specification). o No particles > (b) (4) micrometers were detected.
Method details	Test species:	3 groups of 5 male Dutch-belted rabbits • ~ 4 months old • 1.8 to 2.3 kg body weight
	Dosing	• Topical ocular OU daily for 5 days • One 40 µl drop per dose
	Dose groups	• Vehicle TID • 0.24% cetirizine hydrochloride QD [96 µg/eye/day] • 0.24% cetirizine hydrochloride TID [288 µg/eye/day]
	Endpoints:	• Daily clinical signs • General ocular examination after each dose for:

		hyperemia, discharge, swelling, and other abnormalities • body weight (pre-dose on D5) • Slit-lamp examination (pre-dose and D5) • Blink rate: after dosing on D1 and D5. Note: it is not clear how long after dosing that blink rate was evaluated [i.e. the duration of activity is unclear]
Results	• No effects apparent for clinical signs, body weight, or slit lamp biomicroscopy	
	White crusting	"Slight white crust on corner of the eye" was observed for : • No eyes on D0 (first day of dosing) or D1 (second days of dosing) • Control: 1/10 eyes on D2, 4/10 eyes on D3, 4/10 eyes on D4 • QD cetirizine: 0/10 eyes on each day • TID cetirizine: 2/10 eyes on D2, 2/10 eyes on D3, 1/10 eyes on D4
	Red conjunctiva	"Slightly red conjunctiva" was observed: • Not on D0 or D1 for any eye • Not observed in control eyes • QD cetirizine: D4 only (3/10 eyes) • TID cetirizine: D4 only (1/10 eyes)
	Blink rates	The authors reported a "trend of higher blink rate" with increasing dose, and this reviewer concurs that a treatment-effect on post-dose blink rate is apparent. • For controls, the range of blinks/minute was 1 to 11. • After cetirizine treatment, the blink rate exceeded the control range in 8/40 measurements (range 1 to 21 blinks/minute). • This increase in blink rate is not clearly adverse. • Note: increased blink rate may have decreased local exposure, and may have increased systemic exposure (i.e. increasing the transfer of test article into the nasolacrimal duct).

6.2.2 Repeat-Dose Toxicity

Study title: 14-day evaluation of the ocular toxicity of two ORA concentrations following multiple topical instillations in the eyes of New Zealand White rabbits

Study no.:	P108003 [Applicant's study # AC170-083]
Study report location:	NDA module 4.2.3.2 Toxicology → Repeat-Dose Toxicity → Rabbit – Topical – Short (\\cdsesub1\evsprod\nda208694\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\report-ac170-083\report-body.pdf)
Conducting laboratory and location:	(b) (4) [redacted]
Report date:	June 24, 2009
Date of study initiation:	January 18, 2008
GLP compliance:	Yes, signed • No information regarding the vehicle composition was provided, this omission is not consistent with GLP. • The pathology report is signed, but has no GLP-compliance or QA statement. Therefore, this reviewer presumes that the histopathology assessment was not conducted under GLP.
QA statement:	Yes, signed • The QA statement notes that the dosing, final report and raw data underwent QAU inspection. The pathology report is not explicitly mentioned.
Drug, lot #:	• Test article 1: cetirizine 0.375% + ketotifen 0.05%, lot# 012508CTA • Test article 2: cetirizine 0.25% + ketotifen 0.05%, lot # 012508CTB

Key Study Findings

- This study tested cetirizine in combination with ketotifen, and histopathology was limited to the eyes and ocular adnexa.
- The results are difficult to interpret, because the presence of ketotifen may have reduced the potential ocular irritation of the cetirizine or vehicle.
- Topical ocular dosing was well-tolerated. Mild-to-moderate hyperemia was observed for some dosed eyes.
- Treatment did not affect IOP, ocular histopathology, or slit lamp evaluations.

Methods	
Doses:	• Untreated control • Vehicle control • Test article 1: Cetirizine 0.375% + ketotifen 0.05% • Test article 2: Cetirizine 0.25% + ketotifen 0.05%
Frequency of dosing:	Left eye (OS) bid (two doses per day, 8 ± 1 hours apart) for 14 days
Route of administration:	Topical ocular dosing using a calibrated pipette
Dose volume:	50 µ
Formulation/Vehicle:	• The vehicle formulation was not provided in the study report, and this is a study limitation See section 2.3 of this review (above) • The vehicle was lot # 012508PLAC, used as provided by the study Sponsor
Species/Strain:	Male NZW rabbits
Number/Sex/Group:	• 2 untreated controls (added late; not dosed concurrent with the other rabbits) • 8 males/dose for the vehicle, Test article 1 and test article 2 groups
Age:	14 to 15 weeks old at start of dosing
Weight:	2.25 to 2.64 kg at start of dosing
Deviation from study protocol:	• This reviewer concludes that that protocol amendments documented in the study report are acceptable, and do not change the overall interpretation of the report. • On D1 only, the right eyes (OD) received the same doses as the left eyes. Therefore, 2 untreated control rabbits were added.

Observations and Results

Mortality

- No early deaths. Rabbits were euthanized on D15.
- Animals were checked for mortality/morbidity twice daily.

Clinical Signs

- Evaluation of clinical signs was limited to gross evaluation for irritation and discomfort for 15 to 30 minutes after the second daily dose.
- The treated left eyes exhibited signs post-dose:
    - Vehicle was occasionally associated with OS mild hyperemia

- The low-dose (cetirizine 0.25% + ketotifen 0.05%) and the high-dose (cetirizine 0.375% + ketotifen) were associated with OS mild-to-moderate hyperemia, more frequently compared to vehicle control.
- No chemosis or discharge was observed for any eyes during the study.

Body Weights

- No remarkable observations were noted.
- Body weight was measured pre-dose, on D1, 7 and 14.

Ophthalmoscopy

- For the vehicle- and test-article treated rabbits (but not the two untreated controls):
  - slit lamp observations (conjunctiva, cornea, pupil, iris, and assessment of the aqueous) were performed on D8 and D15.
  - Intraocular pressure (IOP) was measured prior to the first dose on D1, and prior to euthanasia on D15
- One eye (1/16) treated with cetirizine 0.25% + ketotifen 0.05% exhibited mild conjunctival congestion on D15.
- No effects on IOP were apparent.

Hematology and Clinical Chemistry

- Animals were fasted overnight prior to the D15 sacrifice. Blood was collected on D15; standard hematology, coagulation, and clinical chemistry endpoints were measured.
- No treatment-related effects were apparent for these endpoints.
- No urinalysis was performed.

Gross Pathology

- Animals were euthanized on D15. The report does not mention gross pathology or organ weight assessment.

Histopathology

- At euthanasia, both eye globes and conjunctiva, and eyelids were preserved, and evaluated microscopically by (b) (4)
- No treatment-related findings were observed.
- The histopathology report is signed, but no claims of GLP compliance or QA are explicitly stated.

Dosing Solution Analysis

- The test article was analyzed on D1, D7 and D14 (results on page 102 of the study report).
- The results appear adequate; no degradation was detected.

6.2.3 Repeat-Dose Toxicity

Study title: 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

Study no.:	09-5210-G1 [Applicant's AC170-084]
Study report location:	NDA module 4.2.3.2 Toxicology → Repeat-Dose Toxicity → Rabbit – Topical – Short (\\cdsesub1\evsprod\nda208694\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\report-ac170-084\report-body.pdf)
Conducting laboratory and location:	(b) (4)
Report date:	November 19, 2010
Date of study initiation:	December 28, 2009
GLP compliance:	Yes, with the exception that the "characterization and stability of the test substance and its mixture with carriers" was not GLP
QA statement:	Yes, signed
Drugs, lot #s:	• Low dose: cetirizine 0.1% / fluticasone 0.005% suspension, lot # ORA091202.VA, pH 6.5 to 7.8. • High-dose: cetirizine 0.25% / fluticasone 0.01% suspension, lot # ORA091130.V1, pH 6.5 to 7.8

Key Study Findings

- Topical ocular dosing with the high-dose (0.25% cetirizine + 0.01% fluticasone suspension) caused slight conjunctival redness after some doses.
  - This effect is consistent with the other nonclinical topical ocular dosing studies.
- Topical ocular dosing with both the low-dose (0.1% cetirizine + 0.005% fluticasone suspension) and the high-dose (0.25% cetirizine + 0.01% fluticasone suspension) was associated with lymphoid depletion of the eyelid conjunctival associated lymphoid tissue (CALT).

  - The study pathologist considered this treatment-related, and attributed the effect to expected pharmacology of fluticasone, because nasal exposure to fluticasone has been associated with depletion of nasal associated lymphoid tissue (NALT). This reviewer considers this attribution reasonable.
  - Notably, the report did not provide tabulated results (summary data or individual animal data) for this finding; this omission is a serious study limitation.
  - Overall, this reviewer concludes that this study identifies a topical ocular no observed adverse effect level (NOAEL) of 0.25% cetirizine. No topical ocular NOAEL can be identified for fluticasone.
- No treatment-related systemic toxicity was apparent. The study was not designed to identify a systemic NOAEL (e.g. full systemic histopathology was not conducted).
- This study report has three additional limitations, that reduce the usefulness of this study to support Zerviate™:
  - The volume of the administered drops was not reported. The lack of drop volume is a minor study limitation, since the systemic effects of cetirizine (and fluticasone) are well-known.
  - The vehicle formulation was not provided in the study report.
  - Fluticasone is a synthetic trifluorinated corticosteroid with anti-inflammatory activity, that binds the glucocorticoid receptor. Multiple fluticasone therapies are approved, for dermal, intranasal, and inhalation use. Theoretically, the presence of fluticasone may have masked irritation caused by cetirizine (or the vehicle).
- TK was not reported for this study.

Methods	
Doses:	• Vehicle • Low-dose: 0.1% cetirizine + 0.005% fluticasone suspension • High-dose: 0.25% cetirizine + 0.01% fluticasone suspension
Frequency of dosing:	Left eye twice daily (OS bid) for 14 days • The bid doses were administered at least 6 hours apart
Route of administration:	Topical ocular dosing
Dose volume:	• 1 drop per dose, administered from a dropper bottle • The drop volume was not reported in the study report, and the Applicant did not provide a volume estimate (e.g. NDA module 2.6.7 Toxicology Tabulated Summary)
Formulation/Vehicle:	The formulation/vehicle was not specified in the study report, and this is an important study limitation. Please see section 2.3 of this review (above).

	• The pH of the vehicle was tested at 7.0 • The osmolality of the vehicle was tested at 290 mOsm/kg • The vehicle had benzalkonium chloride and disodium edetate dehydrate, but the amounts were not reported (pdf page 318)
Species/Strain:	Dutch-Belted rabbits (*Oryctolagus cuniculus*)
Number/Sex/Group:	• Main-groups: 6/sex/dose (necropsy on D15) • Recovery groups: 3 males, control and high-dose groups only (necropsy on D29)
Age:	At least 11 weeks old
Weight:	1.5 to 2.15 kg
Deviation from study protocol:	• Although the protocol specified histopathology for both eyes, only the treated eye (OS) was evaluated microscopically. This is a study limitation. • This reviewer concludes that the protocol deviations recorded in the study report are minor, and do not affect interpretation of the study

Observations and Results

Mortality

- No early deaths occurred.
- Animals were checked twice daily for moribundity and mortality.

Clinical Signs

- Clinical observations were made once daily.
- The only remarkable clinical signs were conjunctival congestion, reported with ophthalmology findings.

Body Weights

- No treatment-related effects on body weight were apparent.
- Body weight was measured once weekly.

Feed Consumption

- No treatment-related effects on food consumption were apparent.
- Food consumption was quantitatively measured every 3 days.

Ophthalmoscopy

- Methods:

- Ophthalmology on both eyes (OU) was conducted pre-dose to screen the rabbits; only animals without eye abnormalities were used. Ophthalmology was performed on D1, D7, D14 and for the recovery animals on D28
- The ophthalmology endpoints evaluated were: slit lamp biomicroscopy, fluorescein staining, fundoscopy, and tonometry.
  - "Specifically, the slit lamp examination looked for alterations in the cornea, conjunctiva, iris, anterior chamber, and lens.
  - The corneal surface was also assessed using fluorescein stain.
  - The retina was examined for gross changes to the retina or optic nerve and noted as normal or abnormal.
  - Eyes were scored using the "Classification system for grading of ocular lesions combined Draize and McDonald-Shadduck scoring systems'.

- Results:
  - The authors concluded that the vehicle may have affected the cornea, and that the conjunctival congestion observed in high-dose males was treatment-related.
  - No posterior-segment findings were noted for any animal (e.g. vitreous, retina, optic nerve).

Table 10: Ophthalmology findings for the 14-day rabbit study (report # 09-5210-G1)

OS bid topical ocular dosing		Conjunctival congestion	Cornea - opacity
Male	Vehicle	0/9	1/9[a]
	0.1% cetirizine + 0.005% fluticasone	0/6	3/6[b]
	0.25% cetirizine + 0.01% fluticasone	3/9[c]	1/9[d]
Female	Vehicle	0/6	2/6[e]
	0.1% cetirizine + 0.005% fluticasone	0/6	3/6[f]
	0.25% cetirizine + 0.01% fluticasone	0/6	1/6[g]

[a] Days 10-27 [b] Days 7, 13, 14 [c] Observed on D1 and D7 [d] Day 21 only
[e] Day 1 and D 7 [f] Days 7, 11-14 [g] Day 7 only

Hematology and Clinical Chemistry

- Animals were fasted overnight prior to euthanasia, and terminal blood samples were collected from the central ear artery (D15 for main-group animals; D29 for recovery animals).
- Standard batteries for hematology, coagulation, and clinical chemistry were assessed.

Urinalysis

- No treatment-related effects on urinalysis endpoints were apparent.
- Urine was collected at euthanasia by cystocentesis. A standard battery of ten endpoints was measured.

Gross Pathology

- No treatment-related gross pathology findings were apparent.
- At euthanasia, all animals underwent gross necropsy, including "examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents."

Organ Weights

- No treatment-related changes in organ weights were apparent.
- At necropsy, the following organs were weighed: adrenal gland, brain, epididymis, heart, kidneys, liver, ovaries, testes, thymus, and uterus.

Histopathology

- The study pathologist was (b) (4). The pathology report was signed. No peer-review was performed.
- Microscopic examination was limited to: kidneys, lungs, nasal turbinate, and eye with optic nerve (specifically reported were: left eyelid, left optic nerve, left iris/ciliary body, left cornea, left conjunctiva, and left retina).
    - The protocol (pdf page 344) specifies histopathology for "both" eyes with optic nerve. However, data were provided only for the left eye. This omission is a minor study limitation.
    - The original protocol specified both eyes with optic nerve (pdf page 344), and gross lesions. Kidneys and lung histopathology was added (by protocol amendment) because gross lesions were observed in these tissues. Nasal turbinates was added "at Sponsor request".
- The standard battery of systemic organs and tissues were collected and preserved, but the other organs were not examined microscopically.
- The study pathologist noted one treatment-related finding, lymphoid depletion of the left eyelid conjunctival associated lymphoid tissue (CALT).
    - The pathologist considered this expected pharmacology of the fluticasone (i.e. steroid activity).
    - Individual animal data were not reported for CALT; the lack of incidence and severity information is a study limitation.

Toxicokinetics

- No TK results are reported in the study report.
    - Blood samples were collected from the low- and high-dose groups on D1 and D14, and the high-dose recovery group on D29.

- The blood samples were sent to [redacted] (b) (4)
- However, no results were provided to the study laboratory. This reviewer did not identify TK results for this study anywhere else in the NDA.

Dosing Solution Analysis

- Certificates of analysis for the vehicle, low-dose solution, and high-dose solution were provided (dated prior to the start of dosing). The amount of active ingredient (cetirizine and fluticasone) was verified.
- No stability or homogeneity information was provided, and this is a minor study limitation.

6.2.4 Repeat-Dose Toxicity

Study title: Six-month repeat-dose toxicity study of cetirizine ophthalmic solution in Dutch-belted rabbits

Study no.:	CB12-5018-O-TX Applicant's study # AC170-157
Study report location:	NDA module 4.2.3.2 Toxicology → Repeat-Dose Toxicity → Rabbit – Topical – Long (\\cdsesub1\evsprod\nda208694\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\report-ac170-157\report-body.pdf)
Conducting laboratory and location:	• [redacted] (b) (4)
Report date:	September 9, 2013
Date of study initiation:	June11, 2012
GLP compliance:	Yes, signed
QA statement:	Yes, signed
Drug, lot #, and % purity:	• Vehicle solution, lot # 1490563 • 0.24% cetirizine ophthalmic solution, lot # 1490564. The amount of cetirizine was 95.2% of nominal, with [redacted] (b) (4) % impurities.

Key Study Findings

- The study design for the GLP ocular toxicology study appears adequate.

- No treatment-related adverse effects were observed. The NOAEL is the high-dose, 0.24% cetirizine dosed OU tid.
    - This dose represents a 1.5-fold exposure margin over the indicated dose (0.24% cetirizine, dosed bid to one or both eyes).
- The incidence of slight corneal fluorescein increased over time in all three groups. No dose-response is apparent; this effect may be due to the vehicle formulation.
- IOP increased after the start of dosing for all three treatment groups; a dose-response was not apparent. Mean IOP was lower at month 6 and month 7. This increase in IOP might be due to the vehicle formulation, or the handling/procedures of the study.

Methods	
Doses and frequency of dosing:	0 or 0.24% cetirizine, dosing for 6 months • The control group (0% cetirizine) was dosed once per day. • The low-dose group (0.24% cetirizine) was dosed once per day. • The high-dose (0.24% cetirizine) was dosed three times per day (tid), at least 4 hours between doses
Route of administration:	Bilateral (OU) topical ocular doses • The vehicle and test article was provided ready-to-use in dropper vials • At dosing, the drop was applied to the conjunctival sac of the eye, and then the eyelids were held closed for approximately 1 second
Dose volume:	• 1 drop per dose • Drop volume was approximately 40 µl
Formulation/Vehicle:	The Applicant reports that the formulation used in this study is the same as commercial drug formulation (see section 2.3 of this review, above) • The authors report (page 14) that the vehicle was "composed of sodium phosphate dibasic, edetate disodium, benzalkonium chloride, glycerin, polyethylene glycol 400, polysorbate 80, and hypromellose with pH adjusted using sodium hydroxide and/or hydrochloric acid." • The authors did not report the amounts of each ingredient. • The pH of the vehicle was 7.3, and the osmolality was 279 mOsm/kg.
Species/Strain:	Dutch-Belted rabbits (*Oryctolagus cuniculus*)
Number/Sex/Group:	• Main-group: 9/sex/dose (necropsy on D182) • Recovery groups: 3/sex for the control and high-dose groups only (necropsy on D310)

Age:	7 to 8 months old at start of dosing
Weight:	2 to 4 kg at start of dosing
Deviation from study protocol:	The deviations documented in the study report are minor, and this reviewer concludes that they did not meaningfully affect the study results.

Observations and Results

Mortality

- No treatment-related early mortality was observed.
- Animals were checked once daily (as part of clinical signs)
- One male (# 209, from the low-dose group) was found dead on D85 while under anesthesia (in preparation for the 3-month blood collection, prior to bleeding).
    - The authors attributed the death to complications from anesthesia.
    - Full necropsy (including the standard panel of systemic tissues) was conducted for rabbit # 209. Mottled lungs were observed grossly, which correlated with microscopic observations of autolysis (all tissues) and lung severe diffuse hemorrhage.
    - This reviewer concurs that this attribution is reasonable, and that the death is not clearly treatment-related.

Clinical Signs

- No treatment-related clinical signs were apparent.
- Clinical observations were made once daily, and included gross observation of the eyes.
- Gross ocular observations were made prior to the first daily dose, and after the first daily dose, as part of the clinical observations.

Body Weights

- No treatment-related effects on body weight or body weight gain were apparent.
- Body weight was measured weekly.

Feed Consumption

- Animals were housed individually, and received a fixed diet of "~175 g of feed per day". Food consumption was measured over one day, once per week

Ophthalmoscopy

- No treatment-related ophthalmic findings were apparent.
- In addition to the gross ocular observations made as part of clinical sign observations, the cornea and conjunctiva were scored weekly using the 'scale for scoring ocular lesions". The scale records conjunctival redness, chemosis, and discharge; and cornea opacity (degree and area of cornea involved).
- Ophthalmology examinations were performed by a board-certified veterinary ophthalmologist:

  - Time points: prior to the start of dosing, monthly (prior to the first daily dose), at the end of dosing, and at the end of recovery.
  - End points: slit lamp biomicroscopy with fluorescein staining, fundoscopy, and tonometry (the latter using a rebound tonometer). Eyes were scored using a modified Hackett-McDonald scale (i.e. additional sections added for the lens, vitreous, and fundus).
- Slight corneal fluorescein staining was observed intermittently across study groups; no dose-response is apparent. The area of involvement was scored 1 (less than 25% area) or 2 (25-50% of area).
  - The study veterinary ophthalmologist did not consider this effect treatment-related.
  - This reviewer notes that the incidence appears to increase over time, peaking at month 3. Therefore, this reviewer attributes this effect to the vehicle formulation.

Table 11: Incidence of slight corneal fluorescein in the 6-month rabbit ocular toxicity study (report # AC170-157)

Time point	Incidence of slight corneal fluorescein (per # of eyes in each group)					
	Control vehicle (qd dosing)		Low-dose (qd dosing)		High-dose (tid dosing)	
	Male	Female	Male	Female	Male	Female
Pre-study	0/24	3/24	0/18	2/18	0/24	2/24
Month 1	1/24	4/24	4/18	6/18	1/24	5/24
Month 2	0/24	1/24	0/18	1/18	3/24	3/24
Month 3	11/24	9/24	4/16	9/18	6/24	12/24
Month 4	7/24	5/24	4/16	6/18	4/24	4/24
Month 5	9/24	8/24	5/16	9/18	7/24	9/24
Month 6 (end of main-study)	4/24	3/24	4/16	5/18	5/24	6/24
Month 7 (end of recovery)	2/6	1/6	0/0	0/0	0/6	3/6

- Intraocular pressure appeared to increase over time (peaking at month 5, and then dropping below baseline levels at month 6).
  - The study veterinary ophthalmologist considered these observations unrelated to treatment, based on the normal range being 7 to 26 mm Hg for Dutch-belted rabbits.

- This reviewer concurs that no cetirizine-related effect is apparent. However, a clear increase is apparent (comparing the pre-study measurement to the Month 1-4 measurements). Tentatively, this observed increased IOP may be due to the vehicle formulation, or due to the handling/procedures.

Table 12: Intraocular pressure results for the 6-month rabbit ocular toxicity study (report # AC170-157)

Time point	Intraocular pressure (mm Hg, both eyes averaged)					
	Control vehicle (qd dosing)		Low-dose (qd dosing)		High-dose (tid dosing)	
	Male	Female	Male	Female	Male	Female
Pre-study	12.3 ± 2.7	15.5 ± 3.8	11.8 ± 2.5	14.8 ± 4.6	11.6 ±2.3	14.4 ±3.0
Month 1	14.7 ± 1.6	15.1 ± 2.0	16.1 ± 2.7	15.5 ± 2.2	16.0 ± 2.0	16.4 ±2.1
Month 2	17.9 ± 1.8	16.9 ±1.5	16.2 ±2.6	15.9 ±1.9	15.6 ± 2.1	17.2 ±2.4
Month 3	17.8 ± 2.3	17.7 ± 1.4	16.0 ± 3.4	16.7 ±2.3	18.0 ± 2.3	18.4 ±3.5
Month 4	18.4 ± 2.3	19.3 ± 2.1	17.5 ±2.5	17.2 ±2.0	18.8 ±1.6	18.8 ±2.6
Month 5	18.2 ±2.7	19.5 ± 2.8	18.6 ± 2.5	17.9 ±1.9	18.9 ±2.2	19.4 ±2.3
Month 6 (end of main-study)	13.6 ±1.8	14.5 ± 2.0	13.5 ± 1.9	12.4 ±2.2	14.3 ± 2.1	15.9 ±2.1
Month 7 (end of recovery)	14.2 ±2.3	14.3 ± 2.5	-	-	16.7 ± 0.6	14.0 ±0.5

Data presented as mean ± standard deviation

Hematology and Clinical Chemistry

- No treatment-related effects on hematology, coagulation, or clinical chemistry were apparent.
- Blood was collected prior to the start of dosing, at month 3, at the end of dosing, and at the end of recovery. The authors report (page 25) that the animals were anesthetized during blood collection (anesthetic injection site on the back).
- Hematology endpoints were: erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, platelet count, total leukocyte count, differential leukocyte count, and reticulocyte count
- Coagulation endpoints were: prothrombin time, and activated partial thromboplastin

- Clinical chemistry endpoints were: blood urea nitrogen, creatinine, glucose, serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase, gamma glutamyltransferase, total bilirubin, sodium, potassium, chloride, calcium, phosphorous, total protein, albumin, globulin, albumin/globulin ration, triglycerides, and cholesterol.

Urinalysis

- No treatment-related effects on urinalysis were apparent.
- Urine samples were collected at necropsy only, and analyzed for visual appearance and color, blood, urobilinogen, bilirubin, protein, nitrite, , ketones, ascorbic acid, glucose, pH, specific gravity, leukocytes and microscopic evaluation.

Gross Pathology

Organ Weights

- No treatment-related organ weight changes were apparent.
- At necropsy, the following were weighed: adrenal glands, brain, heart, kidneys, liver with gall bladder, lung with bronchi, pituitary gland, uterus, ovaries, epididymis, prostate, seminal vesicles, testes, spleen, submandibular gland, thymus, and thyroid/parathyroid.

Histopathology

- The pathologist concluded “There were no treatment-related histopathologic lesions in the eyes, conjunctiva or adnexa in either the vehicle or high-dose group indicating that the test article appears to be well tolerated under the conditions of this study.” This reviewer concurs. Notably, all ocular tissues were graded normal.
    - The standard battery of systemic organs was collected and preserved.
    - Histopathological assessment was limited to the eye (cornea, iris, retina, optic nerve, conjunctiva, lids, and Harderian/lacrimal gland) for the control and high-dose group (i.e. but not the low-dose group). Histopathology was performed for all observed gross lesions.
- The study pathologist was (b) (4). The pathology report has signed GLP-compliance and QA statements. No histopathology peer review is recorded.
- Results:

Toxicokinetics

- Blood samples were collected for TK on the first day of dosing, and at 1, 3 and 6 months: pre-dose and after the first dose at 5 and 30 minutes, 1, 2, 3,4 ,6 and 8 hours.

  - For the high-dose group, the 4-hour time point collection was performed prior to the second dose, and the 8-hour time point collection was performed prior to the third dose.
  - Blood was shipped to a bioanalytical laboratory, (b) (4) This laboratory provided a bioanalytical report (appendix E of the study report), with signed GLP and QA statements.
  - The data were analyzed by (b) (4) This laboratory provided a toxicokinetic report (appendix F of the study report), with signed GLP and QA statements.
- The Cmax and AUC data show increases from D1 to month 1 (but not thereafter). The report notes (pdf page 28) that coated syringes were used on D1, but not thereafter. The author speculates that the coating may have caused low readings on D1.
- The authors considered the median TK parameters "more representative of data than the means"
- Comparing qd with tid dosing, the AUC was increased with tid dosing, but the C_{max} was not.
- The T_{max} means ranged from 0.3 to 2 hours.
- The serum elimination half-life ($t_{1/2}$) was calculated for the qd group only; the means ranged from 1.66 to 2.75 hours

Table 13: TK median results for the 6-month rabbit ocular toxicity study (report # AC170-157)

time	Parameter	Median values			
		Low-dose (qd dosing)		High-dose (tid dosing)	
		Male	Female	Male	Female
Day 1	C_{max} (ng/ml)	27.0	37.6	30.8	30.1
	$AUC_{0\text{-last}}$ (ng*h/ml)	58.8	64.7	73.1	97.9
Month 1	C_{max} (ng/ml)	37.4	46.5	41.2	52.5
	$AUC_{0\text{-last}}$ (ng*h/ml)	106	123	148	191
Month 3	C_{max} (ng/ml)	48.7	62.9	43.7	48.8
	$AUC_{0\text{-last}}$ (ng*h/ml)	108	111	131	163
Month 6	C_{max} (ng/ml)	36.5	44.9	37.9	51.2
	$AUC_{0\text{-last}}$ (ng*h/ml)	81.7	99.8	121	159

Table 14: TK mean results for the 6-month rabbit ocular toxicity study (report # AC170-157)

time	Parameter	Mean values			
		Low-dose (qd dosing)		High-dose (tid dosing)	
		Male	Female	Male	Female
Day 1	T_{max} (hr)	1	0.4	0.3	2
	C_{max} (ng/ml)	24.6	38.5	29.0	35.5
	$AUC_{0\text{-last}}$ (ng*h/ml)	49.7	77.8	67.9	104
	$T_{1/2}$ (hr)	1.90	1.66	NC	
Month 1	T_{max} (hr)	0.5	0.3	0.7	0.3
	C_{max} (ng/ml)	38.4	51.3	67.2	56.2
	$AUC_{0\text{-last}}$ (ng*h/ml)	101	145	174	193
	$T_{1/2}$ (hr)	2.52	1.98	NC	
Month 3	T_{max} (hr)	0.5	0.3	0.2	2
	C_{max} (ng/ml)	50.3	57.9	45.2	93.3
	$AUC_{0\text{-last}}$ (ng*h/ml)	123	119	130	209
	$T_{1/2}$ (hr)	2.15	2.23	NC	
Month 6	T_{max} (hr)	0.5	0.3	0.3	0.3
	C_{max} (ng/ml)	37.2	48.0	39.3	49.6
	$AUC_{0\text{-last}}$ (ng*h/ml)	89.7	106	122	166
	$T_{1/2}$ (hr)	2.12	2.75	NC	

NC: elimination half-life not calculated for the tid dose group.

Dosing Solution Analysis

- The vehicle and 0.24% cetirizine solutions were provided by the study sponsor ready-to-use in 5 ml dropper bottles. The vials were stored at room temperature, protected from light.
- Dose analysis was conducted prior to the start of dosing, at month 3, and at the end of dosing (month 6). The amounts of cetirizine and BAK, and the pH, were stable over this period.

7 Genetic Toxicology

- No genetic toxicology study reports were submitted to the NDA. The labeling for NDA 019835 for Zyrtec® (cetirizine hydrochloride) tablets summarizes genetic toxicology data, and this NDA relies on the Agency's previous finding of safety for NDA 019835, as reflected in the drug's approved labeling.
- The Applicant's literature references (NDA module 4.3) included a paper by Vlastos et al.[41] This paper reports that cetirizine was positive in an *in vitro* micronucleus assay using human peripheral leukocytes.

- Review of the paper was unable to determine whether the test method was adequate. The OECD guidance[42] notes, "Care should be taken to avoid conditions that could lead to artifactual positive results which do not reflect the genotoxicity of the test chemicals. Such conditions include changes in pH or osmolality, interaction with the cell culture medium or excessive levels of cytotoxicity." The authors report that cetirizine was cytotoxic under the conditions tested.
- The Applicant (NDA module 2.6.6 Toxicology Written Summary) did not proposed to summarize this paper's results in the label, because the concentrations tested were too high to be directly relevant to systemic exposure following topical ocular dosing.
- Based on the weight of available evidence (for genotoxicity, including negative *in vivo* micronucleus results, and for carcinogenicity), and uncertainties regarding the test methods used for Vlastos et al., this reviewer concludes that these *in vitro* micronucleus results do not warrant inclusion in labeling at this time.
- Note: Vlastos et al. does not use any trade name for cetirizine. The test article was supplied by UCB. The Applicant submitted this NDA under 505(b)(2), listing Zyrtec (NDA 019835). The labeling[43] for NDA 019835 explicitly states that the drug product is "marketed by UCB".

8 Carcinogenicity

No carcinogenicity studies were submitted to the NDA. The labeling for NDA 019835 for Zyrtec® (cetirizine hydrochloride) tablets summarizes rodent carcinogenicity data, and this NDA relies on the Agency's previous finding of safety for NDA 019835, as reflected in the drug's approved labeling.

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[41] Vlastos D, Stephanou G. 1998. Effects of cetirizine dihydrochloride on human lymphocytes in vitro: micronucleus induction. Evauation of clastogenic and aneugenic potential using CREST and FISH assays. Arch. Dermatol. Res. 290:312-318.
[42] Organization for Economic Cooperation and Development (OECD) 487. 2016. OECD guideline for the testing ofchemicals. In vitro mammalian cell micronucleus test. Access online via: http://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm
[43] NDA 019835's 2002 labeling accessed via: http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19835s15,%2020346s8lbl.pdf

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No fertility or early embryonic development studies were submitted to the NDA. The labeling for NDA 019835 for Zyrtec® (cetirizine hydrochloride) tablets summarizes nonclinical fertility data, and this NDA relies on the Agency's previous finding of safety for NDA 019835, as reflected in the drug's approved labeling.

9.2 Embryonic Fetal Development

No embryofetal development (EFD) studies were submitted to the NDA. The labeling for NDA 019835 for Zyrtec® (cetirizine hydrochloride) tablets summarizes EFD data, and this NDA relies on the Agency's previous finding of safety for NDA 019835, as reflected in the drug's approved labeling.

9.3 Prenatal and Postnatal Development

- No prenatal and postnatal development (PPND) studies were submitted to the NDA.
- The labeling for approved cetirizine products does not summarize any PPND data.
- Notably, the P/T review for NDA 19835 documents the review of a Segment III (peri- and post-natal reproduction study) in CD-1 mice (report # T-28) with cetirizine administered by oral gavage. Evaluation of the P/T review did not identify any potential concerns for topical ocular dosing of cetirizine. Although the basis for omitting the results of this study from labeling was not identified, P/T defers to the precedent set by the previous P/T review.
- At the pre-NDA meeting, the Applicant proposed to not conduct PPND studies to support this indication, and DTOP concurred.

11 Integrated Summary and Safety Evaluation

11.1 Cetirizine's mechanism of action

- 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.

- The Applicant did not provide new nonclinical information regarding the mechanism of action. Rather, the Applicant relied upon the Agency's findings for a listed drug, Zyrtec® (NDA 019835), as reflected in the drug's approved labeling.
- This reviewer understands that the clinical data submitted to NDA 208694 confirm this mechanism of action; P/T defers to the Clinical discipline regarding the review of clinical results.

11.2 P/T summary for topical ocular cetirizine

- The initiation of clinical trials under IND 108558 relied upon the 14-day topical ocular rabbit study (report # 09-5210-G1; AC170-084) and the oral cetirizine data (Wild, IND 108558, 9/21/2010). The 6-month topical ocular toxicity study (report # AC170-157) was submitted to support the Phase 3 trials.
- The Applicant submitted a rabbit ocular distribution study (report # 2307-001). Following a single topical ocular dose, cetirizine distribution was: cornea > eyelids > conjunctiva > iris/ciliary body > nictitating membrane > sclera > aqueous humor > retina/choroid > lacrimal gland (w/ harderian gland) > optic nerve > lens > vitreous humor > plasma. Topical ocular dosing resulted in low but detectable levels in plasma.
- The 5-day ocular toxicity study in rabbits (report # 170-156) associated the vehicle formulation with increased incidence of slight white crusting. Cetirizine (0.24%, qd or tid) was associated with increased incidence of slightly red conjunctiva and increased blinking.
- Repeat-dose ocular toxicity studies in rabbits tested cetirizine in combination with ketotifen (report # AC170-083) and fluticasone (report # AC170-084). Cetirizine exposure was associated with hyperemia.
- The chronic (6-month) topical ocular toxicity study in rabbits (report # AC170-157) tested cetirizine 0.24% (qd or tid). No effects attributable to cetirizine were detected; the high dose is the ocular no observed adverse effect level NOAEL). All three treatment groups (i.e. including the vehicle control group) exhibited increases in the incidence of slight corneal fluorescein and increased intraocular pressure (IOP). It is not clear whether these effects are (at least partially) due to the vehicle, or (at least partially) due to the handling and procedures.

11.3 ADME/TK background

As noted above, the Applicant submitted this NDA under the 505(b)(2) pathway, listing NDA 019835 (Zyrtec®). The most recent (pre-OTC) labeling is dated March 17, 2004[44].

Data from the NDA 019835 (i.e. orally-administered cetirizine) provide helpful context:

- "**Absorption**: Cetirizine was rapidly absorbed with a time to maximum concentration (T_{max}) of approximately 1 hour following oral administration of tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (C_{max}) of 311 ng/mL was observed. No accumulation was observed.
- "Cetirizine pharmacokinetics were linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of cetirizine exposure (AUC) but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food."
- "**Distribution**: The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed."
- **"Metabolism**: A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.
- **"Elimination**: The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min."

11.4 The local (topical ocular) exposure margin is 1.5 x

- The rabbit topical ocular toxicity studies provide a local (topical ocular) safety margin of 1.5-fold, over the clinical exposure. This reflects the difference between bid patient dosing, versus tid nonclinical dosing.
- Zerviate™ is 0.24% cetirizine (b) (4) The draft labeling dosage and administration of "one drop in each affected eye twice daily".
- The dose of 0.24% cetirizine tid was the NOAEL for both the 5-day topical ocular rabbit study (report # AC170-156) and the 6-month topical ocular rabbit study (report # AC170-157).
- Note: the measured drop size for Zerviate™ was 31 to 37 µl. The drop size used for the 5-day rabbit study was 40 µl, and the drop size for the 6-month rabbit

[44] NDA 019835, labeling accessed via: http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/19835slr016,21150slr005,30346slr011_zyrtec_lbl.pdf

study was “approximately 40 µl”. The 1.5-fold estimate ignores the difference in drop size (which may provide an additional safety margin).

Table 15: Local exposure margin comparison for cetirizine ophthalmic solution 0.24%

	Cetirizine ophthalmic solution	# of drops/dose	# of doses per eye per day	Exposure margin from the clinical dose
Clinical dosing	0.24%	1 per eye	Labeled dose = 2	1 x
5-day rabbit topical ocular toxicity study	0.24%	1 per eye	NOAEL = 3	1.5 x
6-month rabbit topical ocular toxicity study	0.24%	1 per eye	NOAEL = 3	1.5 x

11.5 From oral cetirizine to ophthalmic cetirizine, the dose margin is 28.2 x

- Comparing the approved oral dose of Zyrtec (10 mg/person/day) to the proposed ophthalmic dose (up to 4 drops/person/day), the exposure margin is 28.15x
- For Zerviate™, the Applicant measured the drop volume; the range was 32.1 to 37.0 µl (NDA module 3.2.P.2, file ‘drop-size-study-report-42-840.pdf’). This review will use 37.0 µl for the exposure margin calculations.
- Zerviate™ is 0.24% cetirizine (b) (4) The draft labeling dosage and administration of “one drop in each affected eye twice daily”. Assuming both eyes are dosed with a total of two 37 µl drops per day, the daily dose
  - = 177.6 µg/eye/day of cetirizine
  - = **355.2 µg/person/day** of cetirizine.

  Assuming the patient body weight is 60 kg, and assuming[45] a k_M body surface area (BSA) conversion factor of 37,

[45] CDER 2005 Guidance for Industry. Estimating the maximum safe starting dose in

  - = 5.92 µg/kg/day of cetirizine
  - = 219.04 µg/m^2/day of cetirizine
  - =0.21904 mg/m^2/day of cetirizine
- As the labeling for NDA 019835 notes, "The recommended initial dose of ZYRTEC is 5 or 10 mg per day in adults". Using the same assumptions (body weight and BSA)
  - = 10 mg/person/day of cetirizine
  - = 0.167 mg/kg/day of cetirizine
  - = 6.167 mg/m^2/day of cetirizine

.

Table 16: Dose margin: comparing oral cetirizine (Zyrtec®) and ophthalmic cetirizine (Zerviate™)

Daily dose of cetirizine from Zyrtec®	Daily dose of cetirizine from Zerviate™	Exposure margin based on administered dose
10 mg	355.2 µg [= 0.3552 mg]	28.153 x

11.6 Human equivalent dose (HED) and exposure margin estimates for labeling

- P/T does not concur with the exposure margin estimates proposed by the Applicant in the draft labeling.
- Review did not identify any calculations, of explanation of the Applicant's approach for converting the nonclinical doses. Back-calculation suggests that:
  - The Zyrtec® labeling may have presumed a patient body weight of 50 kg; the exposure margins are reported on a BSA basis.
  - The Applicant's method of calculating the exposure margins is not entirely clear. The Applicant appears to have estimated doses based on mg/kg (not mg/m^2), assuming a drop volume of 40 µl.
- As noted above (section 11.5), P/T's approach is to calculate exposure margins based on BSA scaling, assuming OU bid dosing, with a drop volume of 37 µl.

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initial clinical trial for therapeutics in adult healthy volunteers. Accessed via: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078932.pdf

Table 17: Exposure margin calculations for labeling

Nonclinical data	Dose (mg/kg)	Conversion factor	Dose (mg/m^2)	Exposure margin reported in the Zyrtec® labeling (based on a clinical dose of 10mg/day)[a]	Applicant's proposed exposure margins for Zerviate™ labeling	P/T Exposure margins (fold-difference from the clinical dose of 0.21904 mg/m^2)
Mice … not teratogenic	96	3	288	40 x	15,000 x	1314.83 x
Rats … not teratogenic	180	6	1080	180 x	35,000 x	4930.61 x
Rabbits … not teratogenic	135	12	1620	220 x	-	7395.91 x
Mice … lactation	96	3	288	40 x	15,000 x	1314.83 x
Fertility and general reproductive performance study in mice	64	3	192	25 x	10,000 x	876.55 x
Carcinogenicity study in rats	20	6	120	15 x (for adults)[b]	3,100 x	547.84 x
Carcinogenicity study in mice	16	3	48	6 x (for adults)[c]	2,500 x	219.14 x
No increase in the incidence of liver tumors was observed in mice	4	3	12	2 x	625 x	54.78 x

[a]The Zyrtec label specifies a daily oral dose of 10 mg for adults and 5 mg for children.
[b] 7x for infants
[c] 3x for infants

11.7 The systemic exposure margin based on PK/TK

- As noted above (in section 11.3 of this review), the NDA 019835 labeling reports that 10 mg oral dose resulted in a clinical C_{max} of 311 ng/mL
- The rabbit single-dose ocular distribution study (report # 2307-001) administered cetirizine 0.24% OU, once (single-dose), twice (bid for one day), or bid for 7 days. The highest mean plasma concentration was 26.28 ng/g (equivalent to ng/ml). This measurement may not be a true C_{max} (i.e. the time points selected may have missed the true C_{max}).

- The short-term topical ocular studies (reports # AC17-0156, AC170-083, and AC170-0845) did not report TK results.

- The rabbit 6-month topical ocular toxicity study (report # AC170-157) reported TK results (Table 13 and Table 14 of this review, above). The study tested cetirizine 0.24% qd and tid; the high-dose (tid) was the NOAEL.

    - The highest mean C_{max} for qd dosing was 57.9 ng/ml.

    - The highest mean mean C_{max} for tid dosing was 67.2 ng/ml.

Table 18: Systemic exposure margin comparisons

Topical ocular OU doses with cetirizine 0.24%	Highest mean C_{max} (ng/ml) value	Exposure margin from the plasma C_{max} of 311 ng/ml for the 10 mg oral dose
Rabbit distribution study	26.28	11.834 x
6-month study, qd dosing	57.9	5.371 x
6-month study, tid dosing	67.2	4.628 x

Note: using the highest mean C_{max} may overestimate the true exposure; therefore these exposure margins are considered protective.

11.8 Status of P/T draft information requests (IRs)

1. P/T had requested that an information request (IR) be sent during the NDA review period. This IR is no longer needed; adequate information was identified in the NDA submission.

- As documented in DARRTS, P/T drafted a comment for the NDA 74-day letter, "1. For nonclinical study reports AC170-083, AC170-084, AC170-156, AC170-157, and 2307-001, provide the concentrations of each component of the formulation used for each test article and placebo group." (McDougal, 5/23/2016, NDA 208694). This comment was discussed at the DTOP filing meeting for NDA 208694.
- This reviewer did not identify communication of this comment – for example, the 74-day letter (Marshall, 6/16/2016) did not include this comment.

2. P/T had requested that the Applicant provide additional supporting safety information. P/T concludes that the information provided is adequate.
   - Under IND 108558, P/T advised the Applicant at the End-of-Phase 2 meeting (Germain, 4/05/2013), "Your application should summarize the oral use of cetirizine from the literature, and we recommend that you summarize the applicability or lack of applicability of oral data to your topical ophthalmic formulation."
   - This advice was reiterated at the pre-NDA meeting (Milstein, 1/14/2015)
   - The Applicant provided 16 papers under NDA module 4.3 (Nonclinical Literature References).
3. Based on P/T advice, the Applicant submitted toxicology study reports for the combination of cetirizine and fluticasone propionate to this NDA. The results of these studies support safety.

(b) (4)

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/s/

ANDREW J MCDOUGAL
09/17/2016

LORI E KOTCH
09/17/2016