CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208694Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 2, 2017
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 208694
Product Name and Strength:	Zerviate (cetirizine) ophthalmic solution, 0.24%
Applicant/Sponsor Name:	Nicox Ophthalmics, Inc
Submission Date:	May 1, 2017
OSE RCM #:	2017-652-1
DMEPA Primary Reviewer:	Madhuri R. Patel, PharmD
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the revised container labels, carton labeling, and Prescribing Information (PI) for Zerviate (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels, carton labeling, and PI for Zerviate is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Patel M. Label and Labeling Review for Zerviate (NDA 208694). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 19. RCM No.: 2017-652.

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/s/

MADHURI R PATEL
05/02/2017

SARAH K VEE
05/02/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 19, 2017
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 208694
Product Name and Strength:	Zerviate (cetirizine) ophthalmic solution, 0.24%
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Nicox Ophthalmics, Inc
Submission Date:	March 8, 2017
OSE RCM #:	2017-652
DMEPA Primary Reviewer:	Madhuri R. Patel, PharmD
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, and Prescribing Information (PI) for Zerviate (NDA 208694), submitted by Nicox Ophthalmics, Inc. on March 8, 2017. The Division of Transplant and Ophthalmology Products (DTOP) requested that DMEPA review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. DMEPA finds the Prescribing Information acceptable from a medication error perspective. However, we note that the carton labeling can be improved to minimize route of administration errors. We also note that NDC numbers are often used as an additional verification prior to drug dispensing in the pharmacy and hence it is an important safety feature. We recommend that the UPC Code either be replaced with or match the NDC number for both the container label and carton labeling. Therefore, we provide recommendations in Section 4.1 for the Applicant to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

4.1 RECOMMENDATIONS FOR NICOX OPHTHALMICS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling
    a. Consider relocating the route of administration statement “For Topical Ophthalmic Use” to the principal display panel (PDP) in in accordance with 21 CFR 201.100(b)(3), such as in the gray empty area. However, please ensure the “Rx Only” remains less prominent than the established name and route of administration per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
    b. Please ensure the box marked “UPC Code” is a barcode referring to the product’s NDC number. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible.

B. Container Label
    a. Please ensure the box marked “UPC Code” is a barcode referring to the product’s NDC number. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zerviate that Nicox Ophthalmics, Inc. submitted on March 8, 2017.

Table 2. Relevant Product Information for Zerviate	
Initial Approval Date	N/A
Active Ingredient	cetirizine
Indication	treatment of ocular itching associated with allergic conjunctivitis
Route of Administration	ophthalmic
Dosage Form	ophthalmic solution
Strength	0.24%
Dose and Frequency	one drop in each affected eye twice daily
How Supplied	white low-density polyethylene multi-dose ophthalmic bottle with a low-density polyethylene dropper tip and a white polypropylene cap. 5 mL fill in a 7.5 mL bottle. 7.5 mL fill in a 10 mL bottle
Storage	Store at 15°C to 25°C (59°F to 77°F).
Container Closure	N/A

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 18, 2017, we searched the L:drive and AIMS using the terms, cetirizine, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 previous reviews. We identified two previous proprietary name reviews not relevant to this review. We also identified 1 previous label and labeling review[a], and we confirmed that most of the previous recommendations were implemented.

[a] Rahimi L. Label and Labeling Review for Zerviate (cetirizine) NDA 208694. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUL 20. RCM No.: 2016-1073.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Zerviate labels and labeling submitted by Nicox Ophthalmics, Inc. on March 8, 2017.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

Carton Labeling

(b) (4)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MADHURI R PATEL
04/19/2017

SARAH K VEE
04/19/2017

Clinical Inspection Summary

Date	September 20, 2016
From	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Susan D. Thompson, M.D., for Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To	DTOP\Team Leader\William Boyd DTOP\Medical Officer\Lucious Lim DTOP\Project Manager\Judit Milstein/June Germain
NDA/BLA #	NDA 208694
Applicant	Nicox Ophthalmics, Inc.
Drug	Zerviate (cetirizine ophthalmic solution) 0.24%
NME (Yes/No)	No
Therapeutic Classification	Priority Review
Proposed Indication(s)	Treatment of ocular itching associated with allergic conjunctivitis
Consultation Request Date	March 23, 2016
Summary Goal Date	September 23, 2016
Action Goal Date	October 3, 2016
PDUFA Date	October 18, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Ackerman and De Castro were inspected in support of this NDA. The inspection of Dr. Ackerman's site is classified No Action Indicated (NAI). Dr. DeCastro took a new job during the study, and the study was taken over by the sub-investigator, Dr. Gail Thorkildsen. The inspection of Dr. DeCastro's site is classified "No Action Indicated (NAI) Pending final classification". Final classification as NAI for Dr. Decastro's clinical site is pending review of the inspection report and issuance of the NAI letter to the investigator.

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

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

Protocol 14-100-0006 was entitled "A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of Cetirizine 0.24% Ophthalmic Solution Used Twice Daily in Healthy Adult Subjects and in Pediatric Subjects with a History or Family History of Atopic Disease (including Allergic Conjunctivitis)", and

Protocol 11-100-0012 was entitled "A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Cetirizine 0.24% Ophthalmic Solution (Formula AFH-002) Compared to Vehicle (Formula AFH-001) in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis".

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

Protocol 14-100-0006

The primary objective of the study was to compare the safety and tolerability of cetirizine 0.24% ophthalmic solution versus its vehicle in healthy adult subjects and in pediatric subjects with a history or family history of atopic disease (including allergic conjunctivitis).

This was a multi-center, double-masked, randomized, vehicle-controlled, parallel-group, safety study with assessments of safety and tolerability at the end of study.

This study was conducted at four centers in the U.S. A total of 512 subjects were assessed for safety and tolerability.

Protocol 11-100-0012

The primary objective of this study was to evaluate the efficacy of cetirizine 0.24% ophthalmic solution compared to vehicle in the prevention of allergen-induced conjunctivitis using the Conjunctival Allergen Challenge (CAC) model.

This was a multi-center, double-masked, randomized, vehicle-controlled, parallel-group, conjunctival allergen challenge (CAC) study.

The primary efficacy measures were:

- Ocular itching evaluated by the subject at 3, 5, and 7 minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 3B and 4

- Conjunctival redness evaluated by the investigator at 7, 15, and 20 minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 3B and 4

This study was conducted at three centers in the U.S. A total of 91 subjects were assessed for safety and efficacy.

3. RESULTS (by site):

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

Compliance Classifications

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

1. Dawn DeCastro, M.D./Gail Thorkildsen, M.D.

At this site for Protocol 14-100-0006, 165 subjects were screened, 154 subjects were enrolled, five subjects discontinued, and 149 subjects completed the study.

The records of eighty subjects were reviewed for informed consent and all appeared to be completed appropriately prior to any study-related testing.

The records of 20 subjects were reviewed for protocol compliance and data audit. There was no evidence of under-reporting of adverse events and the safety endpoints were verified against the data listings.

Dr. Torkildsen, the sub-investigator for this study, assumed responsibility for the conduct of the study upon Dr. DeCastro's departure.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Stacey Ackerman, M.D.

At this site for Protocol 11-100-0012, 63 subjects were screened, 27 subjects failed screening, and 36 subjects were randomized and completed the study

Informed consent forms were completed appropriately by all randomized subjects prior to any study-related testing.

Review of the records for randomized subjects included, but was not limited to, financial disclosure, IRB and monitor documentation, training records, source documents, screening and enrollment, the primary efficacy endpoint, pregnancy test logs, drug instillation logs, adverse events, concomitant therapies, protocol deviations, and test article accountability and storage.

A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., for
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.\NDA 208694
DTOP\Division Director\Renata Albrecht
DTOP\Team Leader\William Boyd
DTOP\Medical Officer\Lucious Lim
DTOP\Project Manager\Judit Milstein\June Germain
OSI\DCCE\Division Director\Ni Khin
OSI\ DCCE\GCPAB\Acting Branch Chief\Susan Thompson
OSI\ DCCE\GCPAB\Team Leader\Janice Pohlman
OSI\ DCCE\GCPAB\Reviewer\Roy Blay
OSI\ DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
09/20/2016

JANICE K POHLMAN
09/20/2016

SUSAN D THOMPSON
09/20/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 20, 2016
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 208694
Product Name and Strength:	Zerviate (Cetirizine) Opthalmic Solution, 0.24%
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Nicox Opthalmics, Inc.
Submission Date:	April 18, 2016 and July 11, 2016
OSE RCM #:	2016-1073
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
DMEPA Acting Team Leader:	Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

The Division of Transplant and Opthalmic (DTOP) requested that we review the proposed carton labeling, container label, and Prescribing Information for Zerviate (cetirizine ophthalmic solution, 0.24%). The Applicant is seeking a 505 (b)(2) approval for the proposed indication of treatment of ocular itching associated with allergic conjunctivitis.

1.1 Regulatory History

Cetirizine Ophthalmic Solution, 0.24% was developed for the proposed indication under IND (b) (4) IND 108558. (b) (4) (b) (4) IND (b) (4) The majority of original studies conducted by Nicox were performed under IND 108558. Under IND 108558, (b) (4)

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Nicox Opthalmics, Inc. has submitted the 505 (b)(2) application indicating a new dosage form of cetirizine which is supplied as a preserved ophthalmic solution in multi-dose bottles. We reviewed the proposed carton and container labeling as well as Prescribed Information and identified areas of improvement from medication error perspectives. We have made our recommendations in section 4 of this review.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed carton labeling, container labels, and prescribing information for Zerviate can improve in areas that are vulnerable to medication error. The recommendations for the Division and Applicant are listed in sections 4.1 and 4.2 of this review.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA concludes that the proposed labeling is vulnerable to confusion, which can lead to medication errors. We have revised the ***Dosage and Administration*** section of the Full Prescribing Information and have provided a detailed summary

A. **Highlights and Prescribing Information Labeling:**

1. Replace "TRADENAME" with the conditionally acceptable name "ZERVIATE" throughout all sections of the prescribing information.

B. **Prescribing Information:**

1. Section 16: HOW SUPPLIED/STORAGE AND HANDLING:

    a. Please revise the error prone abbreviation of "cc" from "7.5 cc bottle" and "10 cc bottle" to read "7.5 mL" and "10 mL" bottle. Use of "cc" instead of "mL" is considered a dangerous symbol by Institute of Safe Medication Practice[1]. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products.

[1]ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2016 Jul 19]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

4.2 RECOMMENDATIONS FOR NICOX OPTHALMIC, INC.

We recommend the following be implemented prior to approval of this NDA:

A) All Carton Labeling: (5 mL and 7.5 mL):

1) As currently presented, the established name (cetirizine ophthalmic solution) lacks prominence commensurate with the proprietary name. Please consider increasing the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2). We suggest you increase the fonts on both proprietary name and established names, or decrease the size of the graphics on the labels so there will be more space available for increasing the prominence of the names. In addition, the current (b) (4) color selected for the established name is hard to read. Please consider choosing a different color in order to enhance the readability of the name.
2) We recommend the "Rx only" statement appear less prominent than other important information (e.g. proprietary name, established name, strength, rout of administration) on the primary display panel.
3) The NDC numbers are denoted by a placeholder (XXXX-XXXX-XX). Please replace and ensure that the NDC package code (last 1-2 digits) are different between the 5 mL container and 7 mL container size.
4) We recommend re-locating the statement "FOR TOPICAL OPHTHALMIC USE" to the Principal Display Panel to ensure this this important information is not overlooked. Please replace with "FOR TOPICAL APPLICATION IN THE EYE".

B) All Container Labels (5 mL and 7.5 mL):

1. **See A.1 through A.3.**

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zerviate that Nicox Opthalmics, Inc. submitted on April 18, 2016 and July 11, 2016.

Table 2. Relevant Product Information for Zerviate (certirizine ophthalmic solution 0.24%)	
Initial Approval Date	N/A
Active Ingredient	Cetirizine
Indication	Ocular itching associated with allergic conjunctivitis
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic solution
Strength	0.24%
Dose and Frequency	One drop in each affected eye twice daily
How Supplied	5 mL and 7.5 mL bottles
Storage	Store at 15°C to 25°C (59°F to 77°F). Keep bottle tightly closed when not in use.
Container Closure	Supplied in a white low-density polyethylene multi-dose ophthalmic bottle with a low-density polyethylene dropper tip and a white polypropylene cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 13, 2016, we searched the L:drive and AIMS using the terms, cetirizine to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified zero previous reviews

APPENDIX C. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Zerviate labels and labeling submitted by Nicox Opthalmic, Inc. on April 18, 2016 and July 11, 2016.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

Carton Labeling 5 mL

(b) (4)

Carton Labeling 7.5 mL:

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LEEZA RAHIMI
07/20/2016

HINA S MEHTA
07/21/2016

DSI CONSULT: Request for Clinical Inspections

Date: May 23, 2015

To: Kassa Ayalew, M.D., Acting Branch Chief, GCPA
Janice Pohlman, MD, Team Lead
Roy Blay, MD, Medical Officer
Division of Good Clinical Practice Compliance
Office of Compliance/CDER

Through: Lucious Lim, MD, Medical Officer, 301-796-0749
Division of Transplant and Ophthalmology Products
William Boyd, MD, Clinical Team Leader, 301-796-0686
Division of Transplant and Ophthalmology Products

From: June Germain, Regulatory Health Project Manager, 301-796-4024
Division of Transplant and Ophthalmology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#:	NDA 208694
Applicant/ Applicant contact information:	Nicox Ophthalmics, Inc. 777 Main St Ste 2160 Fort Worth, Texas 76102 Michael V.W. Bergamini, PhD Chief Scientific Officer/Executive Vice President (b) (6) Office (secondary): 817.529.9300 Fax: 817.612.6766 Email: bergamini@nicox.com
Drug:	Zerviate (cetirizine ophthalmic solution) 0.24%
NME:	No
Review Priority:	Yes
Study Population includes < 17 years of age:	Yes
Is this for Pediatric Exclusivity:	Yes

Proposed Indication:	treatment of ocular itching associated with allergic conjunctivitis.
PDUFA:	10/18/2016
Action Goal Date:	10/3/2016
Inspection Summary Goal Date:	9/16/2016

II. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Randomized	Indication
DSI Choice	Study 14-100-0006	512 subjects (341 active; 171 vehicle)	treatment of allergic conjunctivitis
DSI Choice	Study 11-100-0012	91 subjects (46 active; 45 vehicle)	treatment of allergic conjunctivitis
DSI Choice	Study 13-100-0002	101 subjects (51 active; 50 vehicle)	treatment of allergic conjunctivitis
DSI Choice	Study 12-100-0006	100 subjects (50 active; 50 vehicle)	treatment of allergic conjunctivitis

III. Site Selection/Rationale

The clinical portion of the application has been preliminarily reviewed, and no issues have been identified to date to suggest a problem with data integrity.

An inspection is requested for at least one site for Study 14-100-0006.

An inspection is also requested for at least one site at either Study 11-100-0012, Study 13-100-0002, or Study 12-100-0006 as your resources permit.

Note that the highest DOMESTIC enroller in 14-100-0006 is: Dawn DeCastro, M.D. (154).

Note that the highest DOMESTIC enroller in 11-100-0012 is: Gail Torkildsen, M.D. (40).

Note that the highest DOMESTIC enroller in 13-100-0002 is: Eugene McLaurin, M.D. (67).

Note that the highest DOMESTIC enroller in 12-100-0006 is: Gail Torkildsen, M.D. (100).

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
__X__ Other (specify): Routine Inspections

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Goal Date for Completion:
We request that the inspections be performed and that the Inspection Summary Results be provided by **September 16, 2016.** We intend to issue an action letter on this application by October 3, 2016. The PDUFA due date for this application is October 18, 2016.

Should you require any additional information, please contact June Germain at 301-796-4024 or Lucious Lim, MD at 301-796-0749.

Additional Information:
This is an electronic NDA. The List and Description of Investigators for the previously identified studies are provided below.

Table 1.11.3-1. Summary of Clinical Study Trial 14-100-0006 Conducted for Cetirizine Ophthalmic Solution, 0.24%			
Site Number	**Principal Investigator**	**Investigative Site**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
1	Dawn DeCastro, MD	Andover Eye Associates 138 Haverhill St Andover, MA 01810 Phone: 978.685.8900 Fax: 978.689.0020	154 (102/52)
2	Edward Meier, MD	Eye Care Associates of Greater Cincinnati 6394 Thornberry Ct, Ste 810 Mason, OH 45040 Phone: 513.770.4020 Fax: 513.770.4021	120 (80/40)
3	Stacey Ackerman, MD	Philadelphia Eye Associates 1703 S. Broad St Philadelphia, PA 19148 Phone: 215.339.8100 Fax: 215.339.0250	115 (77/38)
4	Eugene Protzko, MD	Seidenberg Protzko Eye Associates 2023 Pulaski Hwy Havre de Grace, MD 20178 Phone: 443.643.4506 Fax: 443.643.4510	123 (82/41)

Table 1.11.3-2. Summary of Clinical Study Trial 11-100-0012 Conducted for Cetirizine Ophthalmic Solution, 0.24%			
Site Number	**Principal Investigator**	**Investigative Site**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
1	Gail Torkildsen, MD	Andover Eye Associates 138 Haverhill St Andover, MA 01810 Phone: 978.685.8900 Fax: 978.689.0020	40 (21/19)
2	Stacey Ackerman, MD	Philadelphia Eye Associates 1703 S. Broad St Philadelphia, PA 19148 Phone: 215.339.8100 Fax: 215.339.0250	36 (18/18)
3	Jack Greiner, DO	Charles River Eye Associates 955 Main St Winchester, MA 01890 Phone: 781.729.3008 Fax: 781.729.2400	15 (7/8)

Table 1.11.3-3. Summary of Clinical Study Trial 13-100-0002 Conducted for Cetirizine Ophthalmic Solution, 0.24%			
Site Number	**Principal Investigator**	**Investigative Site**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
1	Eugene McLaurin, MD	Total Eye Care 6060 Primacy Pkwy, Ste 200 Memphis, TN 38119 Phone: 901.761.4620 Fax: 901.761.4629	67 (34/33)
2	Mark Bergmann, MD	Eye Care Associates of Greater Cincinnati 2859 Boudinot Ave, Ste 301 Cincinnati, OH 45238 Phone: 513.661.3566 Fax: 513.661.6469 **Current Address:** Apex Eye 6507 Harrison Ave, Ste E Cincinnati, OH 45247 Phone: 513.661.3566 Fax: 513.661.6469	22 (11/11)
3	Edward Meier, MD	Eye Care Associates of Greater Cincinnati 6394 Thornberry Cot, Ste 810 Mason, OH 45040 Phone: 513.770.4020 Fax: 513.770.4021	12 (6/6)

Table 1.11.3-4. Summary of Clinical Study Trial 12-100-0006 Conducted for Cetirizine Ophthalmic Solution, 0.24%			
Site Number	**Principal Investigator**	**Investigative Site**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
1	Gail Torkildsen, MD	Andover Eye Associates 138 Haverhill St Andover, MA 01810 Phone: 978.685.8900 Fax: 978.689.0020	100 (50/50)