CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 1, 2018

To: Lois Almoza, M.S.
Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 210913**
. **CEQUA™ (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use**

OPDP has reviewed the proposed carton and container labeling submitted for consult on July 17, 2018, for CEQUA™ (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use. Our review is based on the version of the proposed carton and container labeling that was emailed to OPDP by Lois Almoza on July 31, 2018 (attached). OPDP does not have any comments on the proposed carton and container labeling.

OPDP comments on the proposed Package Insert (PI) were provided under separate cover on July 31, 2018.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
08/01/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 31, 2018

To: Lois Almoza, M.S.
Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 210913**
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OPDP comments on the proposed Carton and Container Labeling will be provided under separate cover.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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CARRIE A NEWCOMER
07/31/2018

Clinical Inspection Summary

Date	May 23, 2018
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	William Boyd, M.D., Clinical Team Leader Lucious Lim, M.D., Clinical Reviewer Lois Almoza, Regulatory Project Manager Division of Transplantation and Ophthalmic Products (DTOP)
NDA#	210913
Applicant	Sun Pharma Global, Inc.
Drug	Cequa (cyclosporine ophthalmic solution) 0.09%
NME	No
Review Priority	Standard
Proposed Indication	To increase tear production (b) (4) associated with keratoconjunctivitis sicca (dry eye)
Consultation Request Date	December 13, 2017
Summary Goal Date	June 8, 2018
Action Goal Date	July 1, 2018
PDUFA Date	August 16, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Evans and Benza were inspected in support of this NDA. 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. The final classification of the inspections of Drs. Evans and Benza was No Action Indicated (NAI).

2. BACKGROUND

The Applicant submitted this NDA to support the use of Cequa (cyclosporine ophthalmic solution) 0.09% for the indication of increased tear production (b) (4) associated with keratoconjunctivitis sicca (dry eye).

Inspections were requested for the following protocols in support of this application:

Protocol OTX-101-2014-001, "A Randomized, Multicenter, Double-Masked, Vehicle-Controlled, Dose-Ranging Study of the Safety and Efficacy of OTX-101 in the Treatment of Keratoconjunctivitis Sicca",

Protocol OTX-101-2016-001, "A Randomized, Multicenter, Double-Masked, Vehicle-Controlled Study of the Safety and Efficacy of OTX-101 in the Treatment of Keratoconjunctivitis Sicca**"**

Protocol OTX-101-2014-001

This study was conducted at 29 study sites in the U.S. enrolling 455 randomized subjects. The primary objective of this dose-ranging study was to evaluate the efficacy and safety of two concentrations of OTX-101 compared with vehicle in the treatment of KCS.

The primary efficacy endpoints were:

- Lissamine green conjunctival staining score in the designated study eye
- Global symptom score

Protocol OTX-101-2016-001

This study was conducted at 45 study sites in the U.S. enrolling 745 randomized subjects. The primary objective of this study was to evaluate the efficacy and safety of OTX-101 0.09% compared with vehicle in the treatment of KCS.

The primary efficacy endpoint was a clinically meaningful improvement (increase of ≥10 mm) from baseline in Schirmer's test (unanesthetized) at Visit 5 (Day 84) based on data averaged for both eyes.

Rationale for Site Selection

The clinical sites of Drs. Evans and Benza were selected for inspection because of their relatively large enrollments and lack of previous inspections.

3. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
Site #6 David Evans Total Eye Care 6060 Primacy Pkwy #200 Memphis, TN 38119	OTX-101-2014-001 Subjects: 42	13-15 Mar 2018	NAI
Site #27 Robert Benza, M.D. 7850 Camargo Road Cincinnati, OH 45247	OTX-101-2016-001 Subjects: 30	22-30 Jan 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

1. David Evans, M.D.

At this site for Protocol OTX-101-2014-001, 47 subjects signed consent forms for the study, 42 subjects were randomized to the study, five subjects were screen failures, one subject withdrew consent, and 41 subjects completed the study. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. All subjects signed and dated the consent forms prior to any study-related procedures.

Source records were both paper and electronic. The electronic source data with the accompanying audit trails for this study were provided to the clinical investigator on a CD. The source records of 21 subjects were compared with line listings. Records reviewed included, but were not limited to, IRB, sponsor, and monitor documentation, financial interest documents, training records, delegation logs, inclusion/exclusion criteria, Case Report Forms (CRFs), primary efficacy endpoints, adverse events, concomitant medications, and drug accountability and disposition.

The primary efficacy endpoint data was verifiable. There was no evidence of underreporting of adverse events.

2. Robert Benza, M.D.

At this site for Protocol OTX-101-2016-001, 32 subjects were screened for the study, 30 subjects were randomized to the study, two subjects were screen failures, and one subject withdrew consent. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. All subjects signed and dated the consent forms prior to any study-related procedures.

Records reviewed included, but were not limited to, IRB, monitor, and sponsor correspondence, Form FDA-1572s, informed consent forms, financial disclosure, subject medical records, inclusion/exclusion criteria, study procedures, adverse events, protocol deviations, case report forms, electronic records, staff training, and test article accountability and storage. The inclusion/exclusion criteria and primary and secondary endpoint data were reviewed for all study subjects.

The primary efficacy endpoint data was verifiable. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

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

CONCURRENCE:

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Phillip Kronstein, M.D.
Team Leader
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Kassa Ayalew, M.D., M.P.H
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cc:
Central Doc. Rm.\NDA 210913
DTOP\Division Director\Renata Albrecht
DTOP\Team Leader\William Boyd
DTOP\Medical Officer\Lucious Lim
DTOP\Project Manager\Lois Almoza
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analyst\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
05/24/2018

PHILLIP D KRONSTEIN
05/28/2018

KASSA AYALEW
05/29/2018

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:	May 2, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 210913
Product Name and Strength:	Cequa (Cyclosporine A) Ophthalmic Solution, 0.09%
Product Type:	Single-ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sun Pharma Global
Submission Date:	October 16, 2017
OSE RCM #:	2017-2223
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

REASON FOR REVIEW

As part of the approval process for Cequa (Cyclosporine A) Ophthalmic Solution, 0.09%, the Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

Sun Pharma Global submitted NDA 210913 to seek marketing approval for Cequa (Cyclosporine A) Ophthalmic Solution, 0.09% indicated to increase tear production (b) (4) associated with keratoconjunctivitis sicca (dry eye).

BACKGROUND/REGULATORY HISTORY (IF APPLICABLE) MATERIALS 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
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

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

1 FINDINGS AND RECOMMENDATIONS

We note that both the sample and trade carton labeling and foil wrappers contain the package type term, 'single-use vial'. To confirm the term 'single-use vial' is appropriate, we consulted the Office of Pharmaceutical Quality (OPQ). OPQ confirmed that the package type term is appropriate because 'single use vial' indicates that the product should be used one time only and discarded immediately after use, regardless of any remaining drug within the vial. This product contains intentional overfill and any remaining drug should be discarded immediately once the proper dose is administered.

Table 2 below includes the identified medication error issues with the submitted prescribing information, label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Transplant and Ophthalmology Products (DTOP)

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1.	Throughout the prescribing information and highlights, the statement (b) (4) [redacted]	Clear disposal instruction is necessary in an effort to prevent reusing an opened vial after one administration.	Change the wording of this statement to "Use immediately after opening and then discard the used vial" as it is written on the carton labeling.

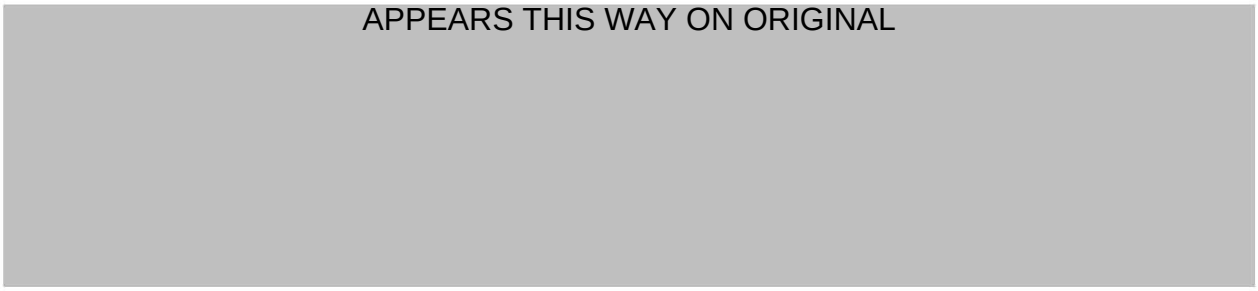
Table 3: Identified Issues and Recommendations for Sun Pharma (entire table to be conveyed to Applicant)

Container Labels			
1.	The strength on the principle display panel '0.09%' is difficult to read.	Failure to clearly display product strength may result in product selection errors.	Change the font of the strength to a font that displays the strength clearly and prominently, to improve readability.
2.	Container label is missing lot number, expiration date and name of manufacturer/packer/ drug distributor.	Lack of lot number or expiration date may result in dispensing errors.	Designate an area for inclusion of the lot number, expiration date and name of manufacturer/packer/ drug distributor on each plastic single-use vial. We also recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.
Carton Labeling (Trade and Sample)			
1.	The strength on the principle display panel	Failure to clearly display product strength may result in product selection errors.	Change the font of the strength to a font that displays the strength clearly

	'0.09%' is difficult to read.		and prominently, to improve readability.
2.	The graphic prior to the proprietary name competes in prominence with the proprietary name 'Cequa'.	To avoid medication errors, the proprietary name, established name, and product strength should be the most prominent information presented on the carton labeling.	Consider removing, relocating or reducing the size of the graphic immediately in front of the proprietary name.
Foil Wrapper (Trade and Sample)			
1.	The strength on the principle display panel '0.09%' is difficult to read.	Failure to clearly display product strength may result in administration errors.	Change the font of the strength to a font that displays the strength clearly and prominently, to improve readability.
2.	Missing designated area for lot number and expiration date.	Lack of lot number or expiration date may result in dispensing errors.	Designate an area for inclusion of the lot number and expiration date. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.
3.	The graphic prior to the proprietary name competes in prominence with the proprietary name 'Cequa'.	To avoid medication errors, the proprietary name, established name, and product strength should be the most prominent information presented on the carton labeling.	Consider removing, relocating or reducing the size of the graphic immediately in front of the proprietary name.

2 CONCLUSION

DMEPA's evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We provided recommendations in Table 2 above for the Division. We also provided recommendations in Table 3 above and ask that the Division conveys the entire table to Sun Pharma so that recommendations are implemented prior to approval of this NDA 210913.



APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Cequa (Cyclosporine A) 0.09% that Sun Pharma submitted on October 16, 2017.

Table 4. Relevant Product Information for Cequa (Cyclosporine A) 0.09%	
Initial Approval Date	N/A
Active Ingredient	Cyclosporine A
Indication	Indicated to increase tear production (b) (4) associated with keratoconjunctivitis sicca (dry eye).
Route of Administration	Intraocular
Dosage Form	Ophthalmic Solution
Strength	0.09%
Dose and Frequency	1 drop into each eye twice daily
How Supplied	Sterile, preservative-free single-use vials. 10 vials are packaged in a foil pouch; (b) (4) 6 pouches are packaged in a box. The entire contents of each box (b) (4) 60 vials) must be dispensed intact.
Storage	(b) (4) °C-25°C ((b) (4) °F-77°F)
Container Closure	(b) (4) vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 24, 2018, we searched the L:drive and AIMS using the terms, Cequa to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not yield any results.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Cequa (Cyclosporine A) 0.09% labels and labeling submitted by Sun Pharma on October 16, 2017.

- Container label
- Carton labeling
- Foil wrapper
- Sample Carton Labeling
- Sample foil wrapper
- Prescribing Information- image not shown

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

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/s/

NASIM N ROOSTA
05/02/2018

OTTO L TOWNSEND
05/02/2018