CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211302Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: July 14, 2020

To: Lois Almoza, Regulatory Health Project Manager, Division of Ophthalmology

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

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for CYSTADROPS® (cysteamine ophthalmic solution) 0.37%, for topical ophthalmic use

NDA: 211302

In response to the Division of Ophthalmology's consult request dated June 30, 2020, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for CYSTADROPS® (cysteamine ophthalmic solution) 0.37%, for topical ophthalmic use.

PI and IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from the Division of Ophthalmology on June 30, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed IFU were sent under separate cover on July 9, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling located in SharePoint on June 30, 2020 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or carrie.newcomer@fda.hhs.gov.

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE A NEWCOMER
07/14/2020 02:37:06 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 9, 2020
To:	Lois Almoza, M.S. Regulatory Project Manager **Division of Ophthalmology (DO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name):	CYSTADROPS (cysteamine ophthalmic solution) 0.37%
Dosage Form and Route:	for topical ophthalmic use
Application Type/Number:	NDA 211302
Applicant:	Recordati Rare Diseases, Inc.

1 INTRODUCTION

On February 28, 2020, Recordati Rare Diseases, Inc., submitted for the Agency's review a Class 2 Resubmission for New Drug Application (NDA) 211302 for CYSTADROPS (cysteamine ophthalmic solution) 0.37%. The proposed indication for CYSTADROPS (cysteamine ophthalmic solution) 0.37% is the treatment of corneal cystine deposits in adults and children with cystinosis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Opthalmology (DO) on June 30, 2020, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for CYSTADROPS (cysteamine ophthalmic solution) 0.37%.

2 MATERIAL REVIEWED

- Draft CYSTADROPS (cysteamine ophthalmic solution) IFU received by the review division on February 28, 2020, and received by DMPP and OPDP on June 30, 2020.
- Draft CYSTADROPS (cysteamine ophthalmic solution) Prescribing Information (PI) received on February 28, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on June 30, 2020.
- Approved CYSTAGON (cysteamine bitartrate) comparator labeling dated June 6, 2007.
- Approved CYSTARAN (cysteamine opthalmic solution) comparator labeling dated April 24, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARIA T NGUYEN
07/09/2020 08:49:55 AM
DMPP-OPDP review of cysteamine opthalmic solution (CYSTADROPS) NDA 211302 IFU

CARRIE A NEWCOMER
07/09/2020 08:51:39 AM

MARCIA B WILLIAMS
07/09/2020 08:53:15 AM

LASHAWN M GRIFFITHS
07/09/2020 09:00:00 AM

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:	April 23, 2020
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 211302
Product Name and Strength:	Cystadrops (cysteamine hydrochloride) ophthalmic solution, 0.37%
Applicant/Sponsor Name:	Recordati Rare Diseases, Inc. (Recordati)
OSE RCM #:	2019-778
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

In this memorandum, we are communicating our previous recommendations for the proposed prescribing information (PI), Instructions for Use (IFU), container label and carton labeling identified on December 6, 2019[a].

2 REGULATORY HISTORY

Recordati submitted their original proposed labels and labeling for NDA 211302 on March 28, 2019 and October 3, 2019. We reviewed the PI, IFU, container labels and carton labeling and identified areas of vulnerability that may lead to medication errors.[a] On January 28, 2020, a Complete Response (CR) Letter was issued for NDA 211302 due to manufacturing deficiencies. Because the CR letter was issued, our label and labeling recommendations were not conveyed to Recordati at that time. On February 28, 2020, Recordati submitted their complete response to the deficiencies included in the CR letter as a Class 2 resubmission.

[a] Roosta, N. Label and Labeling Review for Cystadrops (NDA 211302). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 6. RCM No.: 2019-784.

3 FINDINGS AND RECOMMENDATIONS

Recordati did not submit new proposed labeling as part of the resubmission. Thus, we reviewed the labeling that was previously submitted. We maintain our previous recommendations and tables 1 and 2 below include the previously identified medication error issues with the submitted PI, IFU, container label and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2, Dosage and Administration, includes (b) (4) ”	This statement could be misinterpreted.	(b) (4)
2.	Section 2, Dosage and Administration, includes instruction to (b) (4) however Section 16 intructs the user to ‘discard 7 days after first opening’.	Proper disposal instructions must be clearly stated in order to avoid administering expired drug.	Disposal instructions in Section 2 should be consistent with the disposal instructions in Section 16 and on the carton labeling. For example, “Discard bottle 7 days after first opening.”
Full Prescribing Information – Section 17 Patient Counseling			
1.	Section 17.1, Storage of Bottles, describes assembly instructions for the glass vial and the PVC dropper applicator. This information is more appropriately placed in	The user must be able to readily access vial assembly instructions within the appropriate section of the PI, in order to prevent administration errors.	Move the instructions for use (or an abbreviated version that would be used by a Health Care Professional) to Section 2, Dosage and Administration in a subsection entitled: Preparation for Administration. Additionally, retain the statement, “Advise the patient to read the FDA-approved

Table 1. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Section 2, Dosage and Administration.		patient labeling (Instructions for Use)."
2.	Section 17.1, Storage of Bottles, contains simplified graphics that do not depict the details and colors of the vial.	It is important that the graphics within assembly instructions illustrate the details of the vial, in order to prevent medication preparation errors.	As stated above, the IFU is not appropriate in section 17.1. If the IFU is retained in this section or relocated to Section 2, consider improving the graphics to include details and the appropriate colors of the vial (also see IFU recommendation below).
Instructions for Use (IFU)			
1.	The IFU contains simplified graphics that do not depict the details and colors of the vial.	It is important that the graphics within assembly instructions illustrate the details of the vial, in order to prevent medication preparation errors.	Consider improving the graphics to include details and the appropriate colors of the vial.

Table 2. Identified Issues and Recommendations for Recordati Rare Diseases, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the National Drug Code (NDC) is denoted by a placeholder (NDC 55292-XXX-XX).		Replace this NDC placeholder with the actual NDC on both the container label and carton labeling, when it is determined.
Container Label			
1.	The container label is missing the linear barcode.	The linear barcode is an important safety feature necessary to correctly identify the product and to help prevent product selection and administration errors.	Per 21 CFR 201.25, the linear barcode must appear on the product container label (as defined by section 201(k) of the FD&C Act (21 U.S.C. 321(k)). In addition, please ensure that the linear barcode on the container label is scannable when placed around the curvature of the vial.

Table 2. Identified Issues and Recommendations for Recordati Rare Diseases, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			In addition, the barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i).
2.	The container label does not contain an 'Rx only' statement.	The 'Rx only' statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Revise the container label to include an *Rx only* statement.
Carton Labeling			
1.	The word "opthalmic" in the statement "for opthalmic use only" on the principal display panel (PDP) is misspelled.	Incorrect spelling of route of administration.	Correct the spelling of the word "opthalmic" to "ophthalmic" on the PDP.

4 CONCLUSION

Our evaluation of the proposed Cystadrops prescribing information (PI), Instructions for Use (IFU), container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 1 for the Division and Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to Recordati Rare Diseases, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDIX A. LABELS AND LABELING

A.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 Cystadrops labels and labeling submitted by Recordati Rare Diseases, Inc..

- Container label received on March 28, 2019
- Carton labeling received on March 28, 2019
- Instructions for Use (IFU) (Image not shown) received on October 3, 2019
- Prescribing Information (Image not shown) received on October 3, 2019

A.2 Label and Labeling Images

Container label

(b) (4)

Carton labeling

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


(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NASIM N ROOSTA
04/23/2020 02:39:34 PM

OTTO L TOWNSEND
04/24/2020 09:55:40 AM

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

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

Memorandum

Date: January 30, 2020

To: Lois Almoza
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

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

Subject: **NDA: 211302**
CYSTADROPS® (cysteamine ophthalmic solution) 0.37%

This memo is in response to the Division of Transplant and Ophthalmology Products (DTOP) labeling consult request dated June 6, 2019. Reference is made to a Complete Response (CR) letter that was issued on January 28, 2020. Therefore, the Office of Prescription Drug Promotion (OPDP) defers comment on the Applicant's labeling at this time. Please send us a new consult request for review of the proposed labeling during subsequent review cycle when the application is otherwise adequate.

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE A NEWCOMER
01/30/2020 11:20:20 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	January 24, 2020
To:	Lois Almoza, M.S. Senior Regulatory Health Project Manager **Division of Ophthalmology (DO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Instructions for Use (IFU)
Drug Name (established name):	CYSTADROPS (cysteamine ophthalmic solution) 0.37%
Dosage Form and Route:	ophthalmic solution
Application Type/Number:	NDA 211302
Applicant:	Recordati Rare Diseases, Inc.

1 INTRODUCTION

On March 28, 2019, Recordati Rare Diseases, Inc. submitted for the Agency's review an original New Drug Application (NDA) 211302 for CYSTADROPS (cysteamine ophthalmic solution) 0.37%. The proposed indication for CYSTADROPS (cysteamine ophthalmic solution) 0.37% is the treatment of corneal cystine deposits in adults and children with cystinosis.

On June 7, 2019, the Division of Ophthalmology (DO) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Instructions for Use (IFU) for CYSTADROPS (cysteamine ophthalmic solution) 0.37% .

This memorandum documents the DMPP review deferral of the Applicant's proposed IFU for CYSTADROPS (cysteamine ophthalmic solution) 0.37% .

2 CONCLUSIONS

Due to outstanding manufacturing facility deficiencies, DO plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D JACKSON
01/24/2020 01:31:44 PM

MARCIA B WILLIAMS
01/24/2020 01:36:21 PM

LASHAWN M GRIFFITHS
01/24/2020 01:48:32 PM

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:	December 6, 2019
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 211302
Product Name and Strength:	Cystadrops (cysteamine hydrochloride) ophthalmic solution, 0.37%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Recordati Rare Diseases, Inc.
FDA Received Date:	March 28, 2019 and October 3, 2019
OSE RCM #:	2019-784
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Cystadrops (cysteamine hydrochloride) ophthalmic solution, the Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed Cystadrops prescribing information (PI), Instructions For Use (IFU), container label and carton labeling for areas of vulnerability that may lead to medication errors.

2 MEDICATION ERROR RISKS ASSOCIATED WITH ASSEMBLY FAILURE

We note that the vial and the dropper must be assembled by the patient. During this process, Cystadrops is in contact with air and can be contaminated by particles. Cystadrops can also be in contact with the hands of the patient which can lead to microbiological contamination of the product and, subsequently, a possible eye infection. If the patient fails to assemble the vial and the dropper, they won't be able to administer the drops, which can lead to medication errors (e.g. missed doses). To address these risks associated with Cystadrops in other countries, the Applicant has included information regarding the user instructions on assembling the device and warning users about potential microbiological contamination in both the PI and IFU. We have evaluated the assembly instructions and associated warnings and believe that they should be sufficient and no additional risk mitigation strategies regarding possible medication errors due to device assembly failure are needed at this time.

3 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
Periodic Safety Update Report (PSUR)	E
Labels and Labeling	F

N/A=not applicable for this review

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

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container label and carton labeling, our 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)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2, Dosage and Administration, includes (b) (4)	This statement could be misinterpreted.	(b) (4)
2.	Section 2, Dosage and Administration, includes instruction to (b) (4) '; however section 16 intructs the user to 'discard 7 days after first opening'.	Proper disposal instructions must be clearly stated in order to avoid administering expired drug.	Disposal instructions in Section 2 should be consistent with the disposal instructions in section 16 and on the carton labeling. For example, "Discard bottle 7 days after first opening."
Full Prescribing Information – Section 17 Patient Counseling			
1.	Section 17.1, Storage of Bottles, describes assembly instructions for the glass vial and the PVC dropper applicator. This information is more appropriately placed in	The user must be able to readily access vial assembly instructions within the appropriate section of the PI, in order to prevent administration errors.	Move the instructions for use (or an abbreviated version that would be used by a Health Care Professional) to section 2, Dosage and Administration in a subsection entitled: Preparation for Administration. Additionally, retain the statement, "Advise

Table 2. Identified Issues and Recommendations for Division of Transplant and Ophthalmology Products (DTOP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Section 2, Dosage and Administration.		the patient to read the FDA-approved patient labeling (Instructions for Use)."
2.	Section 17.1, Storage of Bottles, contains simplified graphics that do not depict the details and colors of the vial.	It is important that the graphics within assembly instructions illustrate the details of the vial, in order to prevent medication preparation errors.	As stated above, the IFU is not appropriate in section 17.1. If the IFU is retained in this section or relocated to Section 2, consider improving the graphics to include details and the appropriate colors of the vial (also see IFU recommendation below).
Instructions For Use (IFU)			
1.	The IFU contains simplified graphics that do not depict the details and colors of the vial.	It is important that the graphics within assembly instructions illustrate the details of the vial, in order to prevent medication preparation errors.	Consider improving the graphics to include details and the appropriate colors of the vial.

Table 3. Identified Issues and Recommendations for Recordati Rare Diseases, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the National Drug Code (NDC) is denoted by a placeholder (NDC 55292-XXX-XX).		Replace this NDC placeholder with the actual NDC on both the container label and carton labeling, when it is determined.
Container Label			
1.	The container label is missing the linear barcode.	The linear barcode is an important safety feature necessary to correctly identify the product and to help prevent product	Per 21 CFR 201.25, the linear barcode must appear on the product container label (as defined by section 201(k) of the FD&C Act (21 U.S.C.

Table 3. Identified Issues and Recommendations for Recordati Rare Diseases, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		selection and administration errors.	321(k)). In addition, please ensure that the linear barcode on the container label is scannable when placed around the curvature of the vial. In addition, the barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i).
2.	The container label does not contain an 'Rx only' statement.	The 'Rx only' statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Revise the container label to include an *Rx only* statement.
Carton Labeling			
1.	The word "opthalmic" in the statement "for opthalmic use only" on the principle display panel (PDP) is misspelled.	Incorrect spelling of route of administration.	Correct the spelling of the word "opthalmic" to "ophthalmic" on the PDP.

5 CONCLUSION

Our evaluation of the proposed Cystadrops prescribing information (PI), Instructions For Use (IFU), container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Recordati Rare Diseases, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Cystadrops that Recordati Rare Diseases, Inc. submitted on March 28, 2019 and October 3, 2019.

Table 4. Relevant Product Information for Cystadrops	
Initial Approval Date	N/A
Active Ingredient	cysteamine hydrochloride
Indication	For the treatment of corneal cycstine crystal deposits in adults and children with cycstinosis.
Route of Administration	Ophthalmic
Dosage Form	Solution
Strength	0.37%
Dose and Frequency	One drop in each eye 4 times daily during waking hours
How Supplied	5 mL sterile solution in a 10 mL amber glass vial closed by a stopper and sealed with aluminum tear-off cap. Each carton is packaged with a PVC dropper applicator.
Storage	Before First Opening: Store in refrigerator 2°C to 8°C (36°F to 46°F). Keep the vial in the outer carton in order to protect from light. After First Opening: Store at (b) (4) 25°C (77°F). Do not refrigerate. Keep the dropper bottle tightly closed in the outer carton in order to protect from light. Discard 7 days after first opening.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 20, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, cystadrops and cysteamine. Our search did not identify any previous relevant reviews.

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

D.1 Methods

To help in our assessment of the risk of product contamination during assembly, on October 25, 2019, we searched FAERS using the criteria in the table below and identified thirteen (13) cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient

information was provided by the reporter.[a] We excluded all 13 cases because none described product contamination during assembly.

Table 5. Criteria Used to Search FAERS	
Initial FDA Receive Dates:	9/1/1998- 10/1/2019
Product Name:	Cysteamine , cysteamine dihydrochloride, cystaran
Product Active Ingredient (PAI):	Cysteamine, cysteamine bitartrate, cysteamine hydrochloride
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	Foreign

D.2 Results

Our search identified 13 cases, of which none of the cases described errors relevant for this review.

[a] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX E. PERIODIC SAFETY REPORTS (PSUR)

On November 6, 2019 we reviewed the 2017-2018 Periodic Safety Report for Cystadrops[b] and did not identify any reports that described product contamination during assembly.

[b] The Periodic Safety Reports are available from file:///M|/DMEPA%20Labeling%20Reviews/Cystadrops/psur-2_19jul17-18jan18.pdf and file:///M|/DMEPA%20Labeling%20Reviews/Cystadrops/psur-3_19jan18-18jul18.pdf

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,[c] along with postmarket medication error data, we reviewed the following Cystadrops labels and labeling submitted by Recordati Rare Diseases, Inc..

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

Container label

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

Carton labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NASIM N ROOSTA
12/06/2019 03:56:12 PM

OTTO L TOWNSEND
12/06/2019 05:14:43 PM