CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213581Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: February 23, 2022

To: Dheera Semidey, Regulatory Project Manager
Division of Ophthalmology (DO)

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: ATROPINE SULFATE OPHTHALMIC SOLUTION, USP 1%, for topical ophthalmic use

NDA: 213581

In response to the Division of Ophthalmology (DO) consult request dated July 28, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for ATROPINE SULFATE OPHTHALMIC SOLUTION, USP 1%, for topical ophthalmic use.

Labeling: OPDP has reviewed the attached proposed product labeling received by electronic mail from DO on February 22, 2022 and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic email from DO on February 22, 2022 and we have no additional comments at this time.

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

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/s/

CARRIE A NEWCOMER
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	November 19, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 213581
Product Name and Strength:	Atropine Sulfate Ophthalmic Solution, USP, 1%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Paragon BioTeck, Inc.
FDA Received Date:	May 26, 2021 and July 23, 2021
OSE RCM #:	2021-1078
DMEPA 1 Safety Evaluator:	Nasim Roosta, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Atropine Sulfate Ophthalmic Solution, USP, the Division of Ophthalmology (DO) requested that we review the proposed prescribing information (PI), container label, carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 213581 is a 505(b)(2) application to reference product Atropine Sulfate Ophthalmic Solution, USP 1% (NDA 206289). Under NDA 206289 Atropine Sulfate Ophthalmic Solution is supplied as multi-dose dropper bottles containing 2 mL, 5 mL, and 15 mL of the solution. Under NDA 213581, Paragon BioTeck, Inc. proposes to market Atropine Sulfate Ophthalmic Solution 1% as single-use containers containing 0.4 mL of a preservative-free formulation of the drug product.

2 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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container label, carton labeling, and foil pouch may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Paragon BioTeck, Inc.

4 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 2. 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 includes the instruction to (b) (4) which could lead to misinterpretation.	(b) (4)	We recommend revising the discard statement to, "Discard the single-use container immediately after use."

5 RECOMMENDATIONS FOR PARAGON BIOTECK, INC.

Table 3. Identified Issues and Recommendations for Paragon BioTeck, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	The name of manufacturer, packer, or distributor of the drug is missing on the container label.	The name of the manufacturer, packer, or distributor is required to appear on the container label per 21 CFR 201.10(i).	Add the name of the manufacturer, packer, or distributor to the container label.
2.	The container label is missing the "Rx Only" statement.	The "Rx Only" statement is required on the drug label in accordance with Section 503(b)(4)(A) of the Federal	Add the "Rx Only" statement on the container label.

Table 3. Identified Issues and Recommendations for Paragon BioTeck, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Food, Drug, and Cosmetic Act.	
Carton Labeling and Foil Pouch			
3.	As currently presented, the route of administration statement "FOR TOPICAL OPHTHALMIC USE. NOT FOR INJECTION." is not included on the principal display panel (PDP) of the carton labeling or the packaging.	The route of administration statement is considered to be "critical information." To avoid medication errors involving wrong route of administration, the route of administration statement should be prominently displayed on the PDP. For more information see *Draft guidance for industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*.[a]	To increase the prominence, we recommend that you relocate the route of administration statement "FOR TOPICAL OPHTHALMIC USE. NOT FOR INJECTION" to the PDP.
4.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges.	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example, "20°C - 25°C (68°F - 77°F)".
Carton Labeling			
5.	The net quantity statement "10 vials" does not specify that	Inconsistency across the labels and labeling could lead to confusion or	Revise the net quantity statement to specify that each vial is "single-use." For example, revise to state:

[a] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Table 3. Identified Issues and Recommendations for Paragon BioTeck, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	each vial is a single-use container.	inadvertent misuse of the vials.	"10 single-use vials"
Foil Pouch			
6.	The foil pouch includes the statement (b) (4)	Based on the terminology used, it is unclear if this statement is intended to direct end-users to the Prescribing Information (b) (4) (b) (4)	Clarify the intent of the statement (b) (4) If the intent is to direct end-users to the Prescribing Information, we recommend you revise and relocate the statement from the principal display panel of the foil pouch to allow space for critical information such as the route of administration.
7.	The lot number and expiration date are not included on the foil pouches.	In instances where the foil pouches are separated from the carton, the lot number and expiration date appearing on the foil pouches might help to mitigate the risk of administering deteriorated drug product.	We recommend including the lot number and expiration date on the foil pouches.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for A that Paragon BioTeck, Inc. submitted on July 23, 2021.

Table 4. Relevant Product Information for Atropine Sulfate Ophthalmic Solution, USP	
Initial Approval Date	N/A
Active Ingredient	Atropine
Indication	Atropine Sulfate Ophthalmic Solution, USP 1% is indicated for: Mydriasis, Cycloplegia, Penalization of the healthy eye in the treatment of amblyopia
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic solution
Strength	1%
Dose and Frequency	• In individuals from three (3) months of age or greater, 1 drop topically to the cul-de-sac of the conjunctiva, forty minutes prior to the intended maximal dilation time. • In individuals 3 years of age or greater, doses may be repeated up to twice daily as needed.
How Supplied	Supplied as an aseptically prepared, sterile, preservative-free solution for topical ophthalmic use supplied as a 0.4 mL fill in a translucent, low-density polyethylene, single-use container. One (1) strip of 5 single-use containers are packaged into a foil pouch. Cartons containing 10 single-use containers (two foil pouches each containing one strip of 5 single-use containers)
Storage	Store at 20°C to 25°C (68°F to 77°F). Store single-use containers in the foil pouches.
Container closure	1 mL low density polyethylene (LDPE) vials (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 18, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, “atropine” and “213581”. Our search identified two previous reviews[b,c], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Rutledge, M. Label and Labeling Review for Isopto Atropine (NDA 208151). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 08. RCM No.: 2016-416.

[c] Kapoor, R. Label and Labeling Review for Atropine Sulfate (NDA 206289). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAR 10. RCM No.: 2013-2669.

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,[d] along with postmarket medication error data, we reviewed the following A labels and labeling submitted by Paragon BioTeck, Inc.

- Container label received on May 26, 2021
- Foil pouch received on May 26, 2021
- Carton labeling received on May 26, 2021
- Single-use containers received on May 26, 2021
- Prescribing Information (Image not shown) received on July 23, 2021, (b) (4)

F.2 Label and Labeling Images

(b) (4)

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

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