CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217064Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum:	September 22, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217064
Product Name, Dosage Form, and Strength:	Ryzumvi (phentolamine) ophthalmic solution, 0.75%
Applicant/Sponsor Name:	Ocuphire Pharma, Inc.
TTT ID #:	2022-2912-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, pouch and carton labeling received on September 15, 2023 and September 21, 2023, for Ryzumvi. The Division of Ophthalmology (DO) requested that we review the revised container label, pouch and carton labeling for Ryzumvi (Appendix A) to determine if they are 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 DISCUSSION

Our recommendation to the Applicant which states to include the statement *"store in foil pouch until ready for use"* on the carton and pouch labeling was not shared with the Applicant. However, our rationale which states "Important information embossed on clear plastic such as Low-density polyethylene (LDPE) containers without color is *"generally illegible"* making it difficult to read, which can lead to medication errors" was conveyed to the Applicant.

DO's rationale for not including our recommendation is that *"This product is utilized by physicians a clinical setting. It is not dispensed to patients. The foil pouch is not resealable."*

[a] Getahun, S. Label and Labeling Review for Ryzumvi (NDA 217064). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUL 14. TTT ID No.: 2022-2912.

Additionally, the Applicant's response to our rationale is *"We acknowledge FDA's comment regarding legibility of embossed text in the container* (b) (4)

(b) (4)

(b) (4) *The information on the vial redundantly appears on the foil pouch and carton."*

We considered the Applicant's response and DO's rationale. From a medication error perspective, we maintain our recommendation to include the statement *"store in foil pouch until ready for use"* as storing the vial in the foil pouch until ready for use may help mitigate risk of medication error due to difficulty reading the product information embossed on clear plastic in instances the vial is stored separated from the foil pouch and carton.

3 RECOMMENDATIONS FOR OCUPHIRE PHARMA, INC.

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

A. We recommend including the statement *"store in foil pouch until ready for use"* on the pouch and carton labeling. Additionally, we recommend this storage information be included in *Section 16 How Supplied/Storage and Handling* of the PI.

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/s/

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

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

Memorandum

Date: September 19, 2023

To: Lois Almoza, Senior Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations for Specialty Medicine (DROSM)

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

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for **RYZUMVI (phentolamine ophthalmic solution) 0.75%, for topical ophthalmic use**

NDA: 217064

Background:

In response to DROSM's consult request dated September 18, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for RYZUMVI (phentolamine ophthalmic solution) 0.75%, for topical ophthalmic use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 5, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on September 5, 2023, and we do not have any comments at this time.

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

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

NDA 217064 – Ryzumvi (phentolamine ophthalmic solution) 0.75%
Carton and Container Comments

FDA Comments:

Container Label, Pouch, and Carton Labeling

1. The format for expiration date is not defined on the container label. Additionally, per 21 CFR 201.17, location and format for expiration date is not specified on the carton and pouch labeling. A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors. Identify the expiration date format you intend to use for the container label. Additionally, per 21 CFR 201.17, specify the location for expiration date on the carton and pouch labeling. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends 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. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.

Pouch and Carton Labeling

2. Revise the package type term [(b) (4)] to "single-patient-use".

3. As currently presented, the intended location of the lot or control number is missing. This information should be present per 21 CFR 201.10(i)(1). Include the product's identifying lot or control number and expiration date per 21 CFR 201.10(i). Additionally, ensure the lot number is clearly differentiated from the expiration date.

4. As currently presented, the statement of dosage reads [(b) (4)] [(b) (4)] The terminology [(b) (4)] and [(b) (4)] are not consistent with the terminology used in the Prescribing Information. For clarity and consistency revise to "Dosage: See Prescribing Information."

5. As currently presented, we note the presence of trailing zero (i.e., [(b) (4)] mg of phentolamine mesylate) on the side panel. Trailing zeroes are error prone and can result in a tenfold misinterpretation. Revise [(b) (4)] mg" to read as [(b) (4)] mg".

6. As currently presented, we note the storage temperature "2°C to 8°C (36°F to 46°F)" is a refrigerator temperature per USP Chapter 659[1] <Packaging and Storage requirements> standards. However, the term "refrigerated" preceding the temperature range is not included. Improper storage of this product could lead to

[1] United States Pharmacopoeia (USP) General Chapter <659> Packaging and Storage Requirements

deteriorated drug medication errors. To provide clarity, revise the storage statement to read, “Store refrigerated at 2°C to 8°C (36°F to 46°F).”

Pouch Labeling

7. As currently presented, a space is not provided for users to write in the date of first opening of the pouch. Lack of an allotted space to write in the date of first opening of the pouch may lead to use beyond (b) (4) days. We recommend including the statement “Date of first opening __/__/__” preceding the statement “After opening the foil pouch, the product should be used within (b) (4) days.”

8. As currently presented, we note important information such as the proprietary name, established name, strength, and route of administration is proposed to be embossed on the clear plastic container (vial). Important information embossed on clear plastic such as Low-density polyethylene (LDPE) containers without color is “generally illegible” making it difficult to read, which can lead to medication errors. See FDA guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*[2]

   Our OPQ colleagues confirmed that CMC data “demonstrated the product is stable when stored in the foil pouch and it is not stable only in the vial.” Storing the vial in the foil pouch until ready for use, may help mitigate risk of medication error due to difficulty reading the product information embossed on clear plastic.

   We recommend including the statement “store in foil pouch until ready for use” in the pouch and carton labeling. Additionally, we recommend this storage information be included in Section 16 How Supplied/Storage and Handling of the PI.

Carton Labeling

9. As currently presented, we note that the product identifier is not included. The Drug supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifier recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following:

[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

NDA 217064 – Ryzumvi (phentolamine ophthalmic solution) 0.75%
Carton and Container Comments

NDC: [insert NDC]
Serial: [insert serial number]
LOT: [insert lot number]
EXP: [insert expiration date]

We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers (July 2021).*[3]

If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder to the carton labeling. Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.

[3] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/productidentifiers-under-drug-supply-chain-security-act-questions-and-answers

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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:	July 14, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217064
Product Name and Strength:	Ryzumvi[a] (phentolamine) ophthalmic solution, 0.75%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Ocuphire Pharma, Inc.
FDA Received Date:	November 28, 2022, and March 16, 2023
TTT ID #:	2022-2912
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD.

[a] The proprietary name for this NDA, Ryzumvi was found conditionally acceptable on February 24, 2023.

1 REASON FOR REVIEW

As part of the approval process for Ryzumvi (phentolamine) ophthalmic solution, the Division of Ophthalmology (DO) requested that we review the proposed Ryzumvi prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 217064 is a 505(b)(2) NDA and the listed drug products are Regitine, NDA 008278 and OraVerse, NDA 022159.

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
Information Request Issued During the Review	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

3 DISCUSSION

Our preliminary review noted that important information such as the proprietary name, established name, strength, and route of administration of the product is proposed to be embossed on the clear plastic container (vial). We know that important information embossed on clear plastic ampule such as Low-density polyethylene (LDPE) without color is *"generally illegible"*[b] making it difficult to read, which can lead to medication errors. We considered the

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

following options to recommend to the Applicant to mitigate the risk of medication errors due to difficulty reading the information on the vial:

- Individually overwrapping each unit so that a legible label is applied to the overwrap
- Adding color to the embossed text to afford legibility of the text
- Including a statement in the labeling that indicates to the user that the vials should be stored in the foil pouch until ready for use

To help inform our review we reached out to our Office of Pharmaceutical Quality (OPQ) colleagues to inquire if the *"Chemistry Manufacturing and Control (CMC) data indicate that there is light sensitivity of the product that would warrant storage of the vials in the original pouch until time of use."* Our OPQ colleagues informed us that the CMC data *"demonstrated the product is stable when stored in the foil pouch and it is not stable only in the vial."* As such, recommendation to include the statement "store in foil pouch until ready for use" to the labeling is reasonable at this time.

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, carton and pouch labeling 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 5 for the Division and in Section 6 for Ocuphire Pharma, Inc..

5 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, we note the presence of trailing zero (i.e., 1.0% of phentolamine mesylate) under Section 11 *Description* of the PI.	Trailing zeroes are error prone and can result in a tenfold misinterpretation.	Revise 1.0% to read 1%.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, we note Section 16 of the PI specifies that one	Relevant administration information should be included in Sections 2 and 17.	Consider including the statements *"One single-dose vial can be used to dose each dilated eye. Discard the single-dose vial immediately after*

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	vial can be used *"to dose both eyes."*		*use"* under Section 2, after the Dosing information for children aged 3 to 11 years. Consider adding similar language to Section 17. For example: *Advise patients that the solution from one single-dose container is to be used immediately after opening. It can be used to dose each affected eye. Discard the single-dose container, including any remaining contents, immediately after administration [see Dosage and Administration (2)].*
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented, the appropriate information to facilitate identification of the proposed dosage form is not included.	A description of identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(4)(ii).	Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57(c)(4)(ii).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented the appropriate information to facilitate identification of the dosage form is not included.	A description of the identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57 (c)(17)(iii).	Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57 (c)(17)(iii).

6 RECOMMENDATIONS FOR OCUPHIRE PHARMA, INC.

Table 3. Identified Issues and Recommendations for Ocuphire Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label, Pouch, and Carton Labeling			
1.	The format for expiration date is not defined on the container label. Additionally, per 21 CFR 201.17, location and format for expiration date is not specified on the carton and pouch labeling.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use for the container label. Additionally, per 21 CFR 201.17, specify the location for expiration date on the carton and pouch labeling. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends 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. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.

Table 3. Identified Issues and Recommendations for Ocuphire Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Pouch and Carton Labeling			
1.	As currently presented, the intended location of the lot or control number is missing.	This information should be present per 21 CFR 201.10(i)(1).	Include the product's identifying lot or control number and expiration date per 21 CFR 201.10(i). Additionally, ensure the lot number is clearly differentiated from the expiration date.
2.	As currently presented, the statement of dosage reads (b) (4) (b) (4)	The terminology (b) (4) (b) (4) and (b) (4) (b) (4) are not consistent with the terminology used in the Prescribing Information.	For clarity and consistency revise to "Dosage: See Prescribing Information."
3.	As currently presented, we note the presence of trailing zero (i.e., (b) (4) mg of phentolamine mesylate) on the side panel.	Trailing zeroes are error prone and can result in a tenfold misinterpretation.	Revise (b) (4) mg to read as (b) (4) mg.
4.	As currently presented, we note the storage temperature "2°C to 8°C (36°F to 46°F)" is a refrigerator temperature per USP Chapter 659[c] <Packaging and Storage requirements> standards. However, the term "refrigerated" preceding the	Improper storage of this product could lead to deteriorated drug medication errors.	To provide clarity, revise the storage statement to read, "Store refrigerated at 2°C to 8°C (36°F to 46°F) (b) (4) (b) (4)

[c] United States Pharmacopoeia (USP) General Chapter <659> Packaging and Storage Requirements

Table 3. Identified Issues and Recommendations for Ocuphire Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	temperature range is not included.		
Pouch Labeling			
1.	As currently presented, a space is not provided for users to write in the date of first opening of the pouch.	Lack of an allotted space to write in the date of first opening of the pouch may lead to use beyond (b) (4) days.	We recommend including the statement "Date of first opening __/__/__" preceding the statement "After opening the product should be used within (b) (4) days."
2.	As currently presented, we note important information such as the proprietary name, established name, strength, and route of administration is proposed to be embossed on the clear plastic container (vial).	Important information embossed on clear plastic such as Low-density polyethylene (LDPE) containers without color is *"generally illegible"* making it difficult to read, which can lead to medication errors. See FDA guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*[d] Our OPQ colleagues confirmed that CMC data *"demonstrated the product is stable when stored in the foil pouch and it is not stable only in the vial."* Storing the vial in the foil pouch until ready for use, may help mitigate risk of	We recommend including the statement *"store in foil pouch until ready for use"* on the pouch and carton labeling. Additionally, we recommend this storage information be included in *Section 16 How Supplied/Storage and Handling* of the PI.

[d] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Table 3. Identified Issues and Recommendations for Ocuphire Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		medication error due to difficulty reading the product information embossed on clear plastic.	
Carton Labeling			
1.	As currently presented, we note that the product identifier is not included.	The Drug supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifier recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] Serial: [insert serial number] LOT: [insert lot number]	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers* (July 2021).[e] If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder to the carton labeling. Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.

[e] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers

Table 3. Identified Issues and Recommendations for Ocuphire Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		EXP: [insert expiration date]	

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Ryzumvi that Ocuphire Pharma, Inc. submitted on November 28, 2022, and the listed drugs (LD).

	Table 4. Relevant Product Information for Listed Drug and Ryzumvi		
Product Name	Oraverse	Regitine	Ryzumvi
Initial Approval Date	June 1, 2011	January 30, 1952	N/A
Active Ingredient	Phentolamine mesylate		
Indication	For adult and pediatric patients ages 3 years and older for reversal of the soft-tissue anesthesia, i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor	For the prevention or control of hypertensive episodes that may occur in a patient with pheochromocytoma as a result of stress or manipulation during preoperative preparation and surgical excision. For the prevention or treatment of dermal necrosis and sloughing following intravenous administration or extravasation of norepinephrine. For the diagnosis of pheochromocytoma by the Regitine blocking test.	For the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof.
Route of Administration	Intraoral submucosal injection	Intravenous or intramuscular	Ophthalmic
Dosage Form	Injection	For injection	Ophthalmic solution

Strength	0.4 mg/1.7 mL	5 mg	0.75%
Dose and Frequency	General dosing information: The recommended dose of OraVerse is based on the number of cartridges of local anesthetic with vasoconstrictor administered: OraVerse should be administered following the dental procedure using the same location(s) and technique(s) (infiltration or block injection) employed for the administration of the local anesthetic. Dosing In Special Populations: In pediatric patients weighing between ≥15 kg and <30 kg, the maximum dose of OraVerse recommend is ½ cartridge (0.2 mg). (Note: Use in pediatric patients under 3 years of age or weighing less than15 kg (33 lbs) is not recommended. A dose of more than 1 cartridge [0.4 mg] of OraVerse has not been studied in children less than 4 years of age.)	For preoperative reduction of elevated blood pressure, 5 mg of Regitine (1 mg for children) is injected intravenously or intramuscularly 1 or 2 hours before surgery and repeated if necessary. During surgery, Regitine (5 mg for adults, 1 mg for children) is administered intravenously as indicated, to help prevent or control paroxysms of hypertension, tachycardia, respiratory depression, convulsions, or other effects of epinephrine intoxication. (Postoperatively, norepinephrine may be given to control the hypotension that commonly follows complete removal of a pheochromocytoma.) Prevention or treatment of dermal necrosis and sloughing following intravenous administration or extravasation of norepinephrine. For Prevention: 10 mg of Regitine is added to each liter of solution containing norepinephrine. The pressor effect of norepinephrine is not affected.	Adults and children aged 12 years and older: Instill 1 to 2 drops in each dilated eye following the completion of the ophthalmic examination or procedure to reverse mydriasis. In children aged 3 to 11 years: Instill 1 drop in each dilated eye following the completion of the ophthalmic examination or procedure to reverse mydriasis

		For Treatment: 5-10 mg of Regitine in 10 mL of saline is injected into the area of extravasation within 12 hours. Diagnosis of pheochromocytoma - Regitine blocking test. Sedatives, analgesics, and all other medications except those that might be deemed essential (such as digitalis and insulin) are withheld for at least 24 hours, and preferably 48-72 hours, prior to the test. Antihypertensive drugs are withheld until blood pressure returns to the untreated, hypertensive level. This test is not performed on a patient who is normotensive. Procedure The patient is kept at rest in the supine position throughout the test, preferably in a quiet, darkened room.	

		Injection of Regitine is delayed until blood pressure is stabilized, as evidenced by blood pressure readings taken every 10 minutes for at least 30 minutes. Five milligrams of Regitine is dissolved in 1 mL of Sterile Water for Injection. The dose for adults is 5 mg: for children, 1 mg. The syringe needle is inserted into the vein, and injection is delayed until pressor response to venipuncture has subsided. Regitine is injected rapidly. Blood pressure is recorded immediately after injection, at 30- second intervals for the first 3 minutes, and at 60-second intervals for the next 7 minutes.	

How Supplied	Injection 0.4 mg/1.7 mL is supplied in a dental cartridge, in cartons of 10 and 50 cartridges. Each cartridge is individual packaged in a separate compartment of a 10-cartridge blister pack. NDC 0362-0101-50 NDC 0362-0101-10	Vials— each containing 5 mg of phentolamine mesylate for injection, USP, and 25 mg of mannitol, USP, in lyophilized form. Cartons of 2 NDC 0083-6830-02	Low-density polyethylene, single-dose vial with a 0.31 mL fill. One strip of 5 single-dose vials is packaged into a foil pouch, with 6 foil pouches in a carton. One single-dose vial should be dispensed for each patient, and it can be used to dose both eyes.
Storage	Controlled room temperature, 20-25°C (68-77°F) with brief excursions permitted between 15-30°C (59-86°F) (see USP Controlled Room Temperature) Protect from direct heat and light. Do not permit to freeze.	Store between 15ºC and 30ºC (59ºF-86ºF). The reconstituted solution should be used upon preparation and should not be stored.	Store at 2°C to 8°C (36°F to 46°F) (b) (4) (b) (4) not to exceed the expiration date printed on the box and pouch. (b) (4) (b) (4) (b) (4) (b) (4) Protect from freezing. After opening the foil pouch the product should be used within (b) (4) days, not to exceed the expiration date printed on the vial. The single-dose vial once opened (b) (4) should be discarded immediately after use.
Container Closure	Cartridge	Vial	Vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 24, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, phentolamine, phentolamine mesylate and 217064. Our search did not identify any previous reviews.

APPENDIX E. INFORMATION REQUEST ISSUED DURING THE REVIEW

On, February 28, 2023, we issued an information request (IR) via email requesting Ocuphire to submit the container (vial) label with intended colors, graphics, etc. as it would appear in its final intended state.

On March 16, 2023, Ocuphire provided response to our IR with a submission of the proposed container label. Additionally, their response clarified that the "*graphic of the vial contained in this submission the text that will appear on the vial tab has been provided using a blue font. This is for illustrative purposes to make the text more readable. On the final vial container, the text will be embossed onto the vial tab and so will appear in clear text with no color.*"

Response to the IR can be accessed in EDR via:
\\CDSESUB1\EVSPROD\nda217064\0005\m1\us\12-cover-letters\cover-letter.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,[f] along with postmarket medication error data, we reviewed the following Ryzumvi labels and labeling submitted by Ocuphire Pharma, Inc..

- Container label(s) received on March 16, 2023
- Pouch labeling received on November 28, 2022
- Carton labeling received on November 28, 2022
- Prescribing Information (Image not shown) received on November 28, 2022, available from: \\CDSESUB1\EVSPROD\nda217064\0001\m1\us\114-labeling\draft\labeling\11413-labelingpdf.pdf

F.2 Label and Labeling Images

(b) (4)

Note: *"the graphic of the vial contained in this submission the text that will appear on the vial tab has been provided using a blue font. This is for illustrative purposes to make the text more readable. On the final vial container, the text will be embossed onto the vial tab and so will appear in clear text with no color."*[g]

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

[g] Cover letter: response to Information Request Labeling (NDA 217064 phentolamine mesylate). Farmington Hills (MI): Ocuphire Pharma, Inc; 2023 MAR 16. Available from: \\CDSESUB1\EVSPROD\nda217064\0005\m1\us\12-cover-letters\cover-letter.pdf

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/s/

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07/14/2023 04:36:04 PM

VALERIE S VAUGHAN
07/14/2023 04:57:59 PM

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: NDA 217064

Application Type: New NDA

Drug Name/Dosage Form: phentolamine mesylate ophthalmic solution

Applicant: Ocuphire Pharma, Inc.

Receipt Date: November 28, 2022

1. Regulatory History and Applicant's Main Proposals

This new drug application (NDA), submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), provides for the use of phentolamine mesylate ophthalmic solution for the treatment of pharmacologically-induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof. The proposed proprietary name, Ryzumvi, is under review by the Office of Surveillance and Epidemiology, with a user fee goal date of February 26, 2023.

2. Review of the Prescribing Information

This review is based on the applicant's Word format of the prescribing information (PI) submitted via email on December 1, 2022. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review. All SRPI format deficiencies of the PI will be conveyed to the applicant during labeling discussions. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required

Selected Requirements of Prescribing Information

• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Selected Requirements of Prescribing Information

Patient Counseling Information Statement in Highlights

NO 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

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DEREK S ALBERDING
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