CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212520Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	June 29, 2020
To:	Jacquelyn Smith, MA Senior 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:	Nyedra W. Booker, PharmD, MPH 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):	UPNEEQ (oxymetazoline hydrochloride ophthalmic solution)
Dosage Form and Route:	for topical ophthalmic use
Application Type/Number:	NDA 212520
Applicant:	RevitaLid, Inc.

1 INTRODUCTION

On September 16, 2019 RevitaLid, Inc. submitted for the Agency's review an original New Drug Application (NDA) 212520 for UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), for topical ophthalmic use. The proposed indication for UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), for topical ophthalmic use is for the treatment of acquired blepharoptosis in adults.

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 Ophthalmology (DO) on December 11, 2019 for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), for topical ophthalmic use.

2 MATERIAL REVIEWED

- Draft UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), for topical ophthalmic use IFU received on September 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 18, 2020.
- Draft UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), for topical ophthalmic use Prescribing Information (PI) received on September 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on June 18, 2020.
- Draft UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), for topical ophthalmic use Prescribing Information (PI) received on September 16, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on June 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%. A reading ease score of 60% corresponds to an 8th grade reading level.

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 have reformatted the IFU document using the Arial font, size 11.

In our collaborative review of the IFU we have:

- 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)

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 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.

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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: June 25, 2020

To: Jennifer Harris, Clinical Reviewer
Division of Ophthalmology (DO)

Jacquelyn Smith, Regulatory Project Manager, (DO)

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

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), 0.1% for topical ophthalmic use

NDA: 212520

In response to the Division of Ophthalmology's consult request dated December 11, 2019, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), 0.1% for topical ophthalmic use.

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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 24, 2020 and are provided below.

Comments on the proposed Instructions for Use (IFU) will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from the Division of Ophthalmology on June 25, 2020, and our comments are provided below.

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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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:	June 5, 2020
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 212520
Product Name and Strength:	Oxymetazoline hydrochloride, ophthalmic solution, 0.1%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	RVL Pharmaceuticals, Inc. [a]
FDA Received Date:	September 16, 2019, May 19, 2020, and May 20, 2020
OSE RCM #:	2019-2002
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

[a] The original NDA was submitted by RevitaLid, Inc. The company name was changed to RVL Pharmaceuticals effective April 6, 2020.

1 REASON FOR REVIEW

As part of the approval process for Oxymetazoline hydrochloride ophthalmic solution, the Division of Ophthalmology (DO) requested that we review the proposed Oxymetazoline hydrochloride prescribing information (PI), Instructions For Use (IFU), single-use container label (engraving), foil pouch labeling, zipper bag labeling, and carton labeling for areas of vulnerability that may lead to medication errors.

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 -N/A
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 FINDINGS AND RECOMMENDATIONS

This oxymetazoline ophthalmic solution will be provided in single-use containers. At the initial phase of our review, we noted that the single-use containers displayed a fixed engraving that read "TEST SAMPLE TEST". We sent an IR on May 19, 2020 requesting that RVL provide a detailed description of the engraving on their intend-to-market single-use containers. In their response, RVL submitted detailed images of their intend-to-market single-use containers, and included the details of the engraving we requested.

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), Instructions For Use (IFU), carton labeling, zipper bag labeling, foil pouch 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 Ophthalmology (DO)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1.	Throughout the PI and IFU, replace the proprietary name placeholder, "PROPRIETARY NAME", with the conditionally acceptable proprietary name, once it is determined.		
2.	The proposed container labels, pouch labeling, zipper bag labeling, and carton labeling include the proposed proprietary name, (b) (4) which was found unacceptable.[b] An alternative proposed proprietary name is currently under review. Once a conditionally acceptable proprietary name is determined, the proprietary name on the container labels, pouch labeling, zipper bag labeling, and carton labeling may need to be revised.		
3.	The established name is presented as the salt form (i.e., oxymetazoline hydrochloride) instead of the active moiety (i.e. oxymetazoline).	According to the USP Salt Policy, when an active ingredient in a drug product is a salt, the name of the active moiety (or neutral form), and not the name of the salt (e.g., "newdrug tablets" instead of "newdrug hydrochloride tablets") should be used.[cd]	We defer to OPQ on the determination of the appropriate established name. If OPQ determines that the established name should follow the USP salt policy (i.e., oxymetazoline), the labeling should be revised accordingly.
Highlights of Prescribing Information			
1.	In the Dosage Forms and Strengths section of the Highlights, the quantity of oxymetazoline HCl is expressed as (b) (4) (b) (4)	The strength for ophthalmic solutions are usually expressed as quantity per mL, instead of (b) (4)	We defer to OPQ on the determination of the appropriate strength presentation.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	In Section 3, the statement (b) (4) includes (b) (4) which is not	Users could overlook the (b) (4) when reading this statement. Additionally, consistency throughout the PI is can help reduce the risk of medication errors.	In Section 3, change the (b) (4) to the word "one". For example: (b) (4)

[b] Roosta, N. Proprietary Name Review for (b) (4) (NDA 212520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 07. Panorama No.: 2020-37930727.

[c] Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf

[d] United States Pharmacopoeia (USP) General Chapter <1121> Nomenclature

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	(b) (4) , in Section 2, Dosage and Administration, of the PI.		
2.	In Section 3, the quantity of oxymetazoline HCl is expressed as (b) (4) (b) (4)	The strength for ophthalmic solutions is usually expressed as quantity per mL, instead of (b) (4)	We defer to OPQ on the determination of the appropriate strength presentation.
Instructions For Use (IFU)			
1.	Under "Preparing to Use Proprietary Name", all bullet points, except the first two bullet points, contain information that is already within the steps for administration patients are required to follow on pages 2-4 of the IFU.		We defer to the Patient Labeling Team (PLT) to determine the appropriate format of the IFU.
2.	The "Using Proprietary Name" and "Disposing of Proprietary Name" sections on page 1 of the IFU contain redundant information that is within the steps for administration on pages 2-4 of the IFU.		We defer to the Patient Labeling Team (PLT) to determine the appropriate format of the IFU.

Table 3. Identified Issues and Recommendations for RVL Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Carton Labeling (trade - 30 count)			
1.	The 30-count trade carton includes the statement, (b) (4)	This is an error, as the 30-count carton is intended for retail sale, (b) (4)	Remove the statement (b) (4) on the 30-count trade carton.
Zipper Bag Labeling – Trade and Sample			
1.	We note that the location of the lot number and expiration date are not indicated.	A lot number statement is required on the labels and labeling when there is sufficient space per 21 CFR 201.10(i)(1) and the product expiration date is also required on the labels and labeling per 21 CFR 201.17.	Label the locations where the lot number and expiration dates will appear. See recommendation below related to expiration date format.

Table 3. Identified Issues and Recommendations for RVL Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	The format for the expiration date is not defined.	Clearly defining the expiration date may minimize confusion and risk for deteriorated drug medication errors.	We note MMM YYYY is the expiration date format you intend to use for the carton an intend to use MMM YY as the format for the vials. Please confirm which expiration date format you intend to use for the container labels (zipper bag).
3.	The storage statement does not include information about excursions outside the recommended storage conditions.	Incomplete storage instructions on the zipper bag labeling could result in improper storage of the drug product resulting in deteriorated product medication errors. We also note this statement is not consistent with the storage statement included in the PI.	For consistency and to address the risk of deteriorated product medication errors, revise the storage statement to include permissible excursions. For example: "Store at 20°C-25°C (68°F-77°F); (b) (4) Protect from excessive heat. Keep out of reach of children."
Foil Pouch Labeling			
1.	The foil pouch does not include a storage statement.	Patients may remove individual foil pouches from the zipper bag and a lack of a storage instructions on the pouch labeling could result in improper storage of the drug product resulting in deteriorated product medication errors.	To address the risk of improper storage that could result in deteriorated product medication errors, add a storage statement. For example: "Store at 20°C-25°C (68°F-77°F); (b) (4) . Protect from excessive heat. Keep out of reach of children."

4 CONCLUSION

Our evaluation of the proposed Oxymetazoline hydrochloride prescribing information (PI), Instructions For Use (IFU), carton labeling, zipper bag labeling and foil pouch 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 RVL Pharmaceuticals, 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 Oxymetazoline hydrochloride that RVL Pharmaceuticals, Inc. submitted on September 16, 2019.

Table 4. Relevant Product Information for Oxymetazoline hydrochloride	
Initial Approval Date	N/A
Active Ingredient	Oxymetazoline HCl
Indication	Acquired blepharoptosis (droopy eyelid)
Route of Administration	Ophthalmic
Dosage Form	solution
Strength	0.1%
Dose and Frequency	1 drop per eye once daily
How Supplied	(b) (4) single use container, individually wrapped in a foil pouch. 15 or 30 per carton
Storage	Controlled room temperature (20ºC - 25ºC), (b) (4) .

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,[e] along with postmarket medication error data, we reviewed the following Oxymetazoline hydrochloride labels and labeling submitted by RVL Pharmaceuticals, Inc..

- Single-use container received on May 20, 2020
- Foil Pouch labeling received May 19, 2020
- Zipper bag labeling received May 19, 2020
- Carton labeling received May 19, 2020
- Instructions for Use (Image not shown) received on September 16, 2019
- Prescribing Information (Image not shown) received on September 16, 2019

F.2 Label and Labeling Images

Single-use Container:

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