CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214028Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: October 19, 2021

To: Diana Willard, CPMS
Division of Ophthalmology (DO)

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for VUITY (pilocarpine hydrochloride ophthalmic solution) 1.25%, for topical ophthalmic use

NDA: 214028

In response to the Division of Ophthalmology (DO) consult request dated March 15, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for VUITY (pilocarpine hydrochloride ophthalmic solution) 1.25%, for topical ophthalmic use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO on October 5, 2021 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor and received by electronic email from DO on October 19, 2021, 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.

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/s/

CARRIE A NEWCOMER
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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:	October 15, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 214028
Product Name and Strength:	Vuity (pilocarpine hydrochloride) ophthalmic solution, 1.25%
Applicant/Sponsor Name:	Allergan
OSE RCM #:	2021-361-1
DMEPA 1 Safety Evaluator:	Nasim Roosta, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 12, 2021 for Vuity. Division of Ophthalmology (DO) requested that we review the revised container label and carton labeling for Vuity (Appendix A) to determine if it is 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 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Roosta, N. Label and Labeling Review for Vuity (NDA 214028). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 AUG 6. RCM No.: 2021-361.

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/s/

NASIM N ROOSTA
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VALERIE S VAUGHAN
10/15/2021 02:41:14 PM

Clinical Inspection Summary

Date	September 17, 2021
From	Roy Blay, Ph.D. Karen Bleich, M.D. Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sonal Wadhwa, M.D., Reviewing M.O. William Boyd, M.D., Supervisory M.O. Diana Willard, Supervisory P.M. Division of Ophthalmology
NDA	214028
Applicant	Abbvie, Inc.
Drug	Pilocarpine hydrochloride ophthalmic solution, 1.25% (AGN-190584)
NME	No
Therapeutic Classification	Cholinergic agonist
Proposed Indication(s)	Treatment of presbyopia in adults
Consultation Request Date	19 Apr 21
Summary Goal Date	22 Oct 21
Action Goal Date	5 Nov 21
PDUFA Date	22 Dec 21

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. David Wirta and Jennifer Kim were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

The Applicant submitted this NDA to support the use of pilocarpine hydrochloride ophthalmic solution, 1.25%, in the treatment of presbyopia in adults.

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

Protocol 1883-301-013 (GEMINI 1): A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

and

Protocol 1883-302-013 (GEMINI 2): A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

The studies are essentially identical Phase 3 multicenter, double-masked, randomized, parallel-group, vehicle-controlled studies in adult subjects meeting the study selection criteria for presbyopia. Subjects are randomized 1:1 to the investigational product (IP) or vehicle dosed once daily, bilaterally, for 30 days. The primary efficacy endpoint is the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular Distance-Corrected Near Visual Acuity (DCNVA) at Day 30, Hour 3.

Protocol 1883-301-013 was conducted at 36 study centers in the U.S. with approximately 300 study subjects. The study began on 21 Dec 2018 and concluded on 31 Oct 2019.

Protocol 1883-302-013 was conducted at 35 study centers in the U.S. with approximately 400 study subjects. The study began on Mar 1, 2019 and concluded on 10 Sep 2020.

Dr. Wirta conducted Protocol 1883-301-013 and Dr. Kim conducted Protocol 1883-302-013. These sites were selected for inspection because of their relatively high enrollment of study subjects. The goal of the inspections of these two sites was the evaluation of study conduct and the verification of the primary efficacy endpoint.

III. Results (by site):

1. **Jennifer L. Kim, MD**
1000 Corporate Center Drive, Suite 100, 120
Morrow, GA 30260

Site: 002
Protocol: 1883-302-013
Inspection Dates: 7/20-23/2021

At this site, 28 subjects were screened, 13 were screen failures, 15 subjects were enrolled, one subject was terminated early due to withdrawal of consent, and 14 subjects completed the study. The data listings for the primary efficacy endpoint (DCNVA), adverse events, and protocol deviations were verified against source records for the 15 enrolled subjects. Study records including financial disclosures, study training, informed consents, medical histories, subject eligibility, study visits and procedures, and IP storage and disposition were reviewed.

The inspection compared the source records as noted above with the data listings and no significant discrepancies were observed. Adherence to the regulations and the investigational plan was adequate.

2. David L. Wirta, MD
520 Superior Avenue, Suite 235
Newport Beach, CA 92663

Site: 014
Protocol: 1883-301-013
Subjects: 45

At this site, 54 subjects were screened, 45 were enrolled and randomized to the study, and 44 subjects completed the study. The data listings for the primary efficacy endpoint and adverse events were verified against source records for 25 of the 45 randomized subjects. These records were also reviewed for adequate informed consent. The records of 15 of the 45 enrolled subjects were also reviewed with respect to randomization, meeting eligibility criteria, reporting of concomitant medications, protocol deviations, and study discontinuations, and IP accountability.

The inspection compared the source records as noted above with the data listings and no significant discrepancies were observed. Adherence to the regulations and the investigational plan was adequate.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
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Office of Scientific Investigations

CC:

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Review Division /Division Director/Wiley Chambers
Review Division /Medical Team Leader/William Boyd
Review Division/MO/ Sonal Wadhwa
Review Division /Project Manager/Diana Willard
OSI/Office Director/David Burrow
OSI/DCCE/Acting Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Karen Bleich
OSI/DCCE/GCP Reviewer/Roy Blay
OSI/ GCP Program Analysts/Yolanda Patague

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/s/

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KASSA AYALEW
09/17/2021 11:45:27 AM

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:	August 6, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 214028
Product Name and Strength:	Vuity (pilocarpine hydrochloride) ophthalmic solution, 1.25%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Allergan
FDA Received Date:	February 22, 2021 and March 19, 2021
OSE RCM #:	2021-361
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 pilocarpine hydrochloride ophthalmic solution, the Division of Ophthalmology (DO) requested that we review the proposed pilocarpine hydrochloride prescribing information (PI), container label, carton labeling and packaging 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

The proposed prescribing information (PI), container label, carton labeling and packaging 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 the proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Allergan.

4 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.	We note that the placeholder, “TRADENAME” is	The proprietary name found conditionally	Replace the placeholder, “TRADENAME”, with the

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	included throughout the PI. However, the proposed proprietary name, "Vuity", was found to be conditionally acceptable on January 11, 2021 and April 23, 2021.[ab]	acceptable, "Vuity", should be used throughout the PI.	conditionally acceptable proprietary name, "Vuity".
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	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, "Store at 15° C -25° C (59° F - 77° F)."

5 RECOMMENDATIONS FOR ALLERGAN

Table 3. Identified Issues and Recommendations for Allergan (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not	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

[a] Getahun, S. Proprietary Name Review for Vuity (IND 122483). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 11. Panorama No. 2020-42375055.

[b] Getahun, S. Proprietary Name Review for Vuity (NDA 214028). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 23. Panorama No. 2021-1044723846.

Table 3. Identified Issues and Recommendations for Allergan (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	included following the first numeric degree measurement in the temperature ranges.		measurement of temperature ranges. For example, "Store at 15° C -25° C (59° F - 77° F).
2.	The net quantity statement on the container labels and carton labeling appears more prominently than the strength statement due to its font size and bolded font.	Post-marketing experience shows that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is more prominent and appears in close proximity to the strength statement.	Decrease the prominence of net quantity statement on the container labels and carton labeling. Additionally, we recommend relocating the net quantity statement away from the strength statement on the container labels.
Container Labels			
1.	As currently presented, the storage statement includes the Fahrenheit temperature range prior to the Centigrade temperature range.	The storage statement on the container labels should match the prescribing information and carton labeling for consistency.	We recommend revising the storage statement to include the Centigrade temperature ranges prior to the Fahrenheit temperature ranges, and to switch the order of the temperature ranges to Centigrade followed by Fahrenheit. For example, "Store at 15° C - 25° C (59° F - 77° F)."
Carton Labeling			
1.	The trade carton labeling does not include the machine readable 2D data matrix barcode product identifier.	The DSCSA requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. See Draft Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act

Table 3. Identified Issues and Recommendations for Allergan (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date]	- Questions and Answers (September 2018).[c] Note that the draft guidance recommends that the human-readable portion be located near the 2D data matrix barcode.
2.	The principal display panel (PDP) of the sample carton labeling includes redundant statements to indicate that the 1.5 mL presentation is a sample not intended for resale.	The redundant "sample" statement creates visual clutter on the PDP and detracts from important product information such as the product name, established name, and strength.	We recommend removing the redundant "sample" statement on the PDP.

[c] 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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for pilocarpine hydrochloride that Allergan submitted on February 22, 2021.

Table 4. Relevant Product Information for Vuity	
Initial Approval Date	N/A
Active Ingredient	pilocarpine hydrochloride
Indication	Treatment of near vision impairment associated with presbyopia.
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic solution
Strength	1.25%
Dose and Frequency	1 drop into each eye once daily.
How Supplied	Commercially Available as: 1 bottle pack (2.5 mL in 5 mL bottle) 3 bottle pack (3 of 2.5 mL in 5 mL bottles) Samples: Sample pack, 1 bottle (1.5 mL in 5 mL bottle)
Storage	(b) (4)
Container Closure	Pilocarpine hydrochloride 1.25% ophthalmic solution is supplied sterile in a colorless low density polyethylene bottle, tip and high impact polystyrene dark green cap in 1.5 mL fill in a 5 mL (physician sample) container and 2.5 mL fill in a 5 mL container (commercial product).

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 pilocarpine hydrochloride labels and labeling submitted by Allergan.

- Container labels received on July 9, 2021
- Carton labeling received on July 9, 2021
- Professional Sample Carton Labeling received on July 9, 2021
- Professional Sample Container Label received on July 9, 2021
- Prescribing Information (Image not shown) received on February 22, 2021, available from: \\CDSESUB1\evsprod\nda214028\0001\m1\us\draft-labeling-text.pdf

F.2 Label and Labeling Images

Container label (trade)

(b) (4)

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

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