CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208552Orig1s000

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

PATIENT LABELING REVIEW

Date:	December 8, 2016
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Rowell Medina, PharmD, BCPS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Silvia Wanis, PharmD, CPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	RHOFADE (oxymetazoline hydrochloride)
Dosage Form and Route:	cream, For topical use only
Application Type/Number:	NDA 208552
Applicant:	Allergan, Inc.

1 INTRODUCTION

On March 23, 2016, Allergan, Inc. submitted for the Agency's review a New Drug Application (NDA) 208552 for RHOFADE (oxymetazoline hydrochloride) cream. The proposed indication is for the treatment topical treatment of persistent facial erythema associated with rosacea 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 Dermatology and Dental Products (DDDP) on November 17, 2016, and May 18, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for RHOFADE (oxymetazoline hydrochloride) cream.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

2 MATERIAL REVIEWED

- Draft RHOFADE (oxymetazoline hydrochloride) cream PPI and IFUs received on November 7, 2016, and received by DMPP and OPDP on November 17, 2016.
- Draft RHOFADE (oxymetazoline hydrochloride) cream Prescribing Information (PI) received on March 23, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 17, 2016.
- Approved MIRVASO (brimonidine) comparator labeling dated July 27, 2016.

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. In our review of the PPI and IFUs the target reading level is at or below an 8th grade 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 reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI and IFUs we:

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

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

4 CONCLUSIONS

The PPI and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFUs are 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 PPI and IFUs.

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
12/08/2016

SILVIA WANIS
12/08/2016

BARBARA A FULLER
12/08/2016

LASHAWN M GRIFFITHS
12/08/2016

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

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

Memorandum

Date: December 5, 2016

To: Dawn Williams, RPM
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Silvia Wanis, PharmD, CPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 208552**
OPDP labeling comments for RHOFADE™ (oxymetazoline) topical cream

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Reference is made to DDDP's May 18, 2016 consult request for OPDP's comments regarding the proposed Package Insert (PI) for Rhofade.

OPDP's comments on the proposed labeling, which are based on the draft version of the PI emailed by Dawn Williams on November 17, 2016, are provided below.

OPDP's review and comments on the proposed PPI and IFU was conducted jointly with the Division of Medical Policy Programs (DMPP). This review will be submitted under separate cover at a later date.

If you have any questions, please feel free to contact me:

Silvia Wanis: 301-796-5198; silvia.wanis@fda.hhs.gov

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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SILVIA WANIS
12/07/2016

CLINICAL OUTCOME ASSESSMENT CONSULT REVIEW

CLINICAL OUTCOME ASSESSMENT (COA) TRACKING NUMBER	AT 2016-094
NDA NUMBER	NDA 208552
LETTER DATE/SUBMISSION NUMBER	March 23, 2016 / SDN 1
PDUFA GOAL DATE	January 24, 2017
DATE OF CONSULT REQUEST	May 13, 2016
REVIEW DIVISION	Division of Dermatology and Dental Products
MEDICAL REVIEWER	Amy Woitach
REVIEW DIVISION PM	Dawn Williams
PRIMARY COA REVIEWER	Yasmin Choudhry
SECONDARY COA REVIEWER	NA
ASSOCIATE DIRECTOR, COA STAFF (ACTING)	Elektra Papadopoulos
REVIEW COMPLETION DATE	December 2, 2016
ESTABLISHED NAME	Oxymetazoline topical cream
TRADE NAME	Rhofade™
SPONSOR	Allergan
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome
ENDPOINT(S) CONCEPT(S)	Facial erythema severity
MEASURE(S)	1. Clinician Erythema Assessment 2. Subject Self-Assessment for Rosacea Facial Redness
INDICATION	Treatment of persistent facial erythema associated with rosacea
INTENDED POPULATION(S)	Adult subjects with persistent rosacea-related erythema

Clinical Outcome Assessment Review
Yasmin Choudhry, M.D.
NDA 208552
Oxymetazoline cream
Clinician Erythema Scale & Subject Self-Assessment for Rosacea Facial Redness

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Dermatology and Dental Products (DDDP) regarding NDA 208552 Oxymetazoline cream for the treatment of persistent facial erythema of rosacea.

The Applicant utilized the following two measures as primary efficacy composite endpoint (i.e., *at least 2-grade improvement in both measures*) in their oxymetazoline confirmatory clinical trials:

1. Clinician Erythema Scale (CEA): A single-item, clinician-reported outcome (ClinRO) measure to assess erythema severity with a photo guide to assess erythema severity.
2. Subject Self-Assessment (SSA) for Rosacea Facial Redness: A single-item, patient-reported outcome (PRO) measure (with a photo guide) to assess erythema severity.

Note that both instruments (CEA and SSA) used the same set of photos. See Section B1.3 for hierarchy of endpoints; Appendix A: CEA; and Appendix B: SSA.

This review focuses on the data submitted within the PRO dossier for the SSA. The sponsor did not provide an evidence dossier for the CEA.

The SSA is not an ideal instrument for a variety of reasons. For example, there were issues with content validity. Majority of patients had difficulty with photograph-sorting exercise largely due to patients matching up response options with more than one category of photographs. Upon reviewing the instrument, it appeared that some of the photographic examples were not appropriate for the grade severity in that they were either milder or more severe than the others.

Additionally, the test-retest scores are suboptimal (ICC-0.58, ICC-0.38) even though we acknowledge that rosacea is difficult to assess because the redness waxes and wanes, and that it is difficult to identify a stable population to assess this measurement property.

The concordance (cross-tabulation on study Day 1; and 28) between the CEA and SSA demonstrated that at Day 1, 72% of the SSA ratings are the same as the CEA ratings. At Day 28, about 50% of SSA ratings are the same as the CEA ratings. On the surface, the percentage of ratings suggests some degree of concordance between the two instruments. However, the concordance statistics (i.e., Cohen's kappa that measures the agreement between two raters who each classify items into mutually exclusive categories) were not provided in the submission. Therefore, the exact degree of concordance between these two instruments is not known (See Section B5 of this review).

For future use in clinical trials, further modification of the SSA (better descriptors, less number of photographs to minimize overlapping) would be advisable to address these issues. Because the same photographs were used in the CEA, the modifications would also apply to the CEA.

The applicant demonstrated statistically significant results for the composite primary endpoint showing a ≥2 grade improvement on both CEA and SSA. (b) (4) . If needed, we suggest the following language to provide a description of the SSA in the oxymetazoline label: *The score changes are based on a single-item patient-reported outcome measure (with sample photographs) that assessed severity of facial redness of rosacea.*

B. CLINICAL OUTCOME ASSESSMENT REVIEW

Materials reviewed:

- Allergan's PRO Dossiers:
    - Subject Self-Assessment for Rosacea Facial Redness (SSA) with Photo guide dated October 30, 2013
    - Symptom- and Satisfaction-Assessments for Rosacea Facial Redness dated January 22, 2016
- May 13, 2016 DDDP Consult
- Previous COA review AT 2013-179; and October 29, 2015 FDA Meeting Minutes

1 CONTEXT OF USE

1.1 Target Study Population and Clinical Setting

The target population was adult patients with persistent facial erythema associated with rosacea. Only patients with baseline scores of 3 (moderate) or 4 (severe) on both scales (CEA and SSA) were eligible for enrollment into the trials.

1.2 Clinical Trial Design, Protocol, and Analysis Plan

The two phase 3 studies (Study 199201-004 & Study 199201-005) for oxymetazoline were multicenter, double-blind, randomized, parallel-group, vehicle-controlled studies.

1.3 Endpoint Positioning

The endpoint model is as follows:

Concepts	Endpoints	Instrument
Primary Efficacy Endpoint		
Erythema severity	Proportion of patients with at least a 2-grade decrease (improvement) on from baseline (pre-dose on day 1) over a 12-hour period, measured at each hour 3, 6, 9, & 12 post-dose on day 29	Clinician Erythema Scale (CEA) + Subject Self-Assessment (SSA) for Rosacea Facial Redness (RFR)
Secondary Efficacy Endpoint		
Erythema severity	Proportion of patients with at least a 2-grade decrease (improvement) from baseline (pre-dose on day 1) over a 12-hour period, measured at each hour 3, 6, 9, & 12 post-dose on day 29	SSA
Erythema severity	Percent change from baseline in facial redness measured at each hour 3, 6, 9, and 12 on day 29	Digital Image Analysis
Satisfaction with treatment	Proportion of patient who report 'satisfied' or 'very satisfied' for Item #9 (*Right now, how satisfied are you with the effect your study medication had on your facial redness?*) at each hour 3, 6, 9, and 12 on day 29	Satisfaction-RFR Follow-up (SAT-RFR-Follow-up)
Burning intensity	Change from baseline in Item #4 (*Right now how much does your face burn because of your facial redness?*)	Symptom Assessment for Rosacea Facial Redness (SA-RFR)
Time to onset	Proportion of patient with at least a 1-grade decrease from baseline at hour 1 post-dose on day 1	SSA

1.4 Labeling or promotional claim(s) based on the COA

Allergan seeks the following labeling claim:

(b) (4)

[redacted]

Table 3: Proportion of Patients Acheiving Composite Primary Endpoint on Day 29

Timepoint (Hour)	Trial 1		Trial 2	
	RHOFADE™ Topical Cream** (N = 222)	Vehicle Cream (N = 218)	RHOFADE™ Topical Cream** (N = 224)	Vehicle Cream (N = 221)
3	12%*	6%	14%*	7%
6	16%*	8%	13%*	5%
9	18%*	6%	16%*	9%
12	15%*	6%	12%*	6%

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

Both, the CEA and the SSA are single item instruments assessing severity of facial erythema (redness) from the clinician's perspective and the patient's perspective respectively.

3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

Clinician Erythema Assessment (CEA):

The CEA is a single-item ClinRO with 5 response options (i.e., 0=Clear skin with no signs of erythema to 4=Severe erythema/fiery redness, and a photo guide (with 20 photos, 4 photos represent each of the five facial redness severity categories). See Appendix A of this review. Details of how this scale was developed were not provided.

Subject Self-Assessment (SSA) for rosacea facial redness:

The SSA is a self-administered electronic tablet device with a single item rated on a 5-point categorical scale (i.e., 0=No signs of unwanted redness to 4=Severe redness). The recall period is 'right now'. The SSA has a photo guide (same as the CEA). See Appendix B of this review.

SSA assessment timing and data collection method: In the phase 3 trials, the SSA was assessed at Screening visit (Day -30 to Day -3); Day 1 (pre-dose); hours 1, 3, 6, 9, and 12 hours (post-dose); Day 15 and 29 (predose); hours 1, 3, 6, 9, and 12 hours post-dose; Day 43 (follow-up); and Day 57 (follow-up and exit). The SSA was to be completed before the investigator performed the CEA. The subject and investigator were not to discuss the subjects' SSA assessment grade.

Scoring algorithm: The SSA item scores were transformed to a 0-100 scale when used as a stand-alone measure (independent from the CEA).

The following two measures were also utilized in the phase 3 studies:

Satisfaction-Assessment for Rosacea Facial Redness (SAT-RFR):

The SAT-RFR is a 10-item questionnaire to assess patient satisfaction with the effects of the study medication on facial redness. The recall period is 'right now' and the response options include *very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied or very satisfied*.

The item of interest (as secondary endpoint) is item #9: *Right now, how satisfied are you with the effect your study medication had on your facial redness?*

Symptom-Assessment for Rosacea Facial Redness (SA-RFR): The SA-RFR has four items grouped into two domains: Skin Appearance and Skin Sensations. The Skin Appearance domain includes two items on Severity/Intensity of Facial Redness and Amount of Redness (Area). The Skin Sensations domain includes two items on Facial Warmth and Facial Burning related to erythema associated with rosacea. The item of interest (as secondary endpoint) is Item 4: *Right now, how much does your face burn because of your facial redness? Does not burn at all; Burns a little; Burns somewhat; Burns quite a bit; and Burns a lot.*

Reviewer comment: Please note that the SAT- and SA-RFR were not considered for further review. [redacted] ***and a cursory review of the SAT-RFR measurement properties indicated that the SAT-RFR did not demonstrate a difference in satisfaction with the effect of medication on rosacea between the study drug and the vehicle.***

4 CONTENT VALIDITY

Allergan's, final SSA conceptual model was a result of an iterative process based on published literature, subject-matter expert input and patient input as described below. A summary of content validity report (provided by [redacted]) is as follows (See SSA Dossier for details):

Subject Self-Assessment (SSA) for Rosacea Facial Redness & Photo guide

The response options for the SSA were initially designed to partly mirror the CEA. Concept elicitation interviews conducted in 21 patients resulted in the draft SSA Version 1. The SSA Version 2 was created after photographs (from the CEA) were added to SSA Version 1. After cognitive interviews were conducted, the instrument name was changed to 'Modified SSA V2'. The Modified SSA V2 was further modified ("unwanted redness" was included in the response option). In Allergan's phase 3 studies, the name SSA was used instead of SSA 2. The name SSA has been used throughout this review.

Photograph sorting exercise:

Photograph-sorting exercise was conducted (as two rounds of cognitive interviews) and patients were asked to rank each of 20 photographs of individuals with rosacea into one of five categories by severity.

In Round 1 of cognitive interviews (n=21), majority of patients labeled each severity grade with the correct response option. However, nine photographs were miscategorized by more than 33.0% of patients. Of these nine photographs, seven were miscategorized into a less severe grade. Most patients (n=14, 66.7%) considered the area of redness when sorting the photographs for the photo numeric guide (consistent with what they were instructed to do).

The most common problem among patients completing the photograph-sorting exercise was difficulty distinguishing between the milder categories (n=6, 28.6%). It appears that issues in labeling photographs with each severity grade were largely due to patients matching up response options with more than one category of photographs.

In Round 2 of the cognitive interviews (n=20), a modified technique for the photograph sorting exercise was used. Patients were asked to sort five photographs at a time using only one photograph from each grade; patients received four sets of five photographs of individuals with rosacea and were asked to rank the photographs within each set, matching the photographs to the severity categories designated by the different response options. Patients ranked each set of five photographs separately and were told that only one photograph may be assigned to each category/response option. This was done in order to provide more data for analysis prior to making a decision on whether to retain or modify the SSA photographs. (b) (4) recommended that the performance of the photo numeric guide should be tested in Allergan's Phase 2b clinical studies.

Results of Round 2 interviews indicate that patients were able to categorize photographs more accurately when asked to categorize only five photographs at a time. Each individual photograph was categorized correctly by at least 75% of patients. However, when asked to put one photograph in each category, 40% (n=8) of patients still miscategorized at least one Grade. More specifically, up to 25.0% of patients (n=5) miscategorized the same Grade 0 and Grade 1 photographs. (b) (4) further recommended that the performance of the photo numeric guide should be tested in Allergan's Phase 2b clinical studies, and that clinical sites (for phase 3 studies) provide detailed patient training on the use of the instrument.

The resulting SSA version was cognitively debriefed in 20 additional patients. All patients interpreted the instructions/items as intended. Patients were also asked to complete the final SSA Version to assess their facial redness on an electronic tablet device (Tablet Kiosk NetSlate Sahara A510T device), using the photo guide for reference. Majority of patients had good understanding of the instructions and the modified response options.

Reviewer comment: This reviewer believes that despite using a different technique (categorizing only five photographs at a time, 40% (n=8) of patients still miscategorized the photographs. We also do not know whether detailed instructions were provided to patients (as advised by (b) (4)) in phase 3 trials.

This reviewer found the photographs to be overlapping as well. For example, one of the four photographs for CEA Scale Grade 2 (mild erythema) could be considered moderate; similarly,

one of the photographs in the CEA Scale Grade 3 (moderate erythema) appears severe to this reviewer.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Subject Self-Assessment (SSA) of Rosacea Facial Redness

The measurement properties of the SSA were evaluated in 356 patients in a US-based, multi-center, randomized, double-blind, vehicle-controlled phase 2b study (Study 199201-002). Patients included in the study were male/female ≥18 years old with moderate to severe facial erythema associated with rosacea (defined as either "more redness than I prefer" or "completely unacceptable redness" on the SSA of Erythema scale as assessed by the patient).

Moderate to severe facial erythema associated with rosacea was defined as a grade of ≥3 on the CEA scale with photo numeric guide as assessed by the investigator and either "more redness than I prefer" or "completely unacceptable redness" on the SSA (initial version) as assessed by the patient.

Demographics and clinical characteristics:

The mean age of patients was 50.0 years (range from 19.0 to 79.0 years); of the 356 patients, majority (91%) were Caucasian, 8% were Hispanic, and 0.30% African American; and majority (80%) of patients were females with 60% being over 45 years of age.

Patients' disease characteristics at baseline (predose) were as follows:

- Based on the CEA: Majority (82%, N 282) of patients had moderate (*marked redness*) erythema and 64 (18%) of patients had severe (*fiery*) erythema.
- Based on the SSA: Majority (70%, N 252) of patients had moderate (*more redness than I prefer*) erythema; 103 (18%) patients had severe (*completely unacceptable*) erythema; and one patient had mild to moderate (*somewhat more redness than I pre*fer) erythema.

Reviewer comment: This reviewer believes that for a validation study, a range of severity levels should have been evaluated.

Two analysis populations were defined to conduct the overall validation (cross sectional) and test-retest (TRT at two timepoints) analyses, respectively. Patients having at least one item response on the SSA evaluated at baseline were included in the cross sectional analysis population. Day 1 (pre-dose) was defined as "Baseline".

Patients having at least one item response on the SSA evaluated at baseline were included in the cross sectional analysis population. The baseline mean SSA scores were 78.10 (SD 11.00).

An item was considered to have a ceiling or floor effect if more than 20% of responses were in the highest or lowest response categories of the SSA. The "Not applicable" response was coded

as missing. Results for the floor and ceiling effects were presented as N, percent floor, and percent ceiling effect per item. No notable floor or ceiling effects were seen for the SSA.

Reliability

Test-retest:

Test-retest determines reproducibility of scores and refers to an instrument's ability to reproduce identical measurements between testing when no change has occurred in the underlying concept.

Test-retest population was defined using two approaches:

- TRT-1 Population: The stable patients for the test-retest analysis were defined as a subset of the cross-sectional population from treatment groups 4 vehicle QD and 8 vehicle BID (assuming that the placebo group is not expected to change due to no drug intervention). Test-retest reliability was assessed between Day 14 (pre-dose) and Day 28 (pre-dose).
- TRT-2 Population: Stable population for test-retest reliability was assessed by including patients who reported the same response on CEA at Day14 (pre-dose) and Day 28 (predose) (i.e., patients who neither improved nor worsened and hence were stable and were defined as TRT-2 Population for all the active treatment groups). For example, if a patient responds "Mild" on Day 14 and "Mild" again on Day 28, then it is assumed that the patient has not changed and hence is stable.

The SSA scores were correlated for two administrations by using Intra-Class Correlation (ICC) coefficients. Results indicated that the ICCs for the two administrations were -0.38 and -0.58.

Reviewer comment: The observed ICC values for test-retest are low. Reliability estimates of >0.7 are generally considered strong. **We agree with the applicant that this may be in part due to the transient nature of rosacea.**

Construct Validity

Construct validity is determined by evidence that relationships among items, domains, and concepts conform to a priori hypotheses concerning logical relationships that should exist with measures of related concepts or scores produced in similar or diverse patient groups. The validity is concluded when the associations between concepts measured by a specified instrument and concepts measured by other instruments are as expected.

Convergent and discriminant validity:

Both SSA and CEA measures were treated as categorical variables and were cross-tabulated with each other to evaluate the pattern of response options for facial redness due to rosacea in each category at Day 1 and Day 28.

From the tables below it appears that, at Day 1, 72% of the SSA ratings are the same as the CEA ratings; at Day 1 all subjects are rated 3 or 4 on both scales due to the trial's entry criteria. At Day 28, about 50% of SSA ratings are the same as the CEA ratings. On the surface, the percentage of ratings suggests some degree of concordance between the two instruments. However, the concordance statistics (i.e., kappa) were not provided.

Table 01.1.9-1 (page 1 of 1)
Distribution of CEA versus SSA-2 at Day 1-predose
(Cross-sectional Analysis Population)

Table of cea_1 by ssa2_1

cea_1(CEA at Day 1) ssa2_1(SSA_2 at Day 1)

Frequency / Percent / Row Pct / Col Pct	0	1	2	3	4	Total
0	0 0.00 . .	0 0.00 . .	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00
1	0 0.00 . .	0 0.00 . .	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00
2	0 0.00 . .	0 0.00 . .	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00
3	0 0.00 0.00 .	0 0.00 0.00 .	14 3.94 4.79 93.33	238 67.04 81.51 84.70	40 11.27 13.70 67.80	292 82.25
4	0 0.00 0.00 .	0 0.00 0.00 .	1 0.28 1.59 6.67	43 12.11 68.25 15.30	19 5.35 30.16 32.20	63 17.75
Total	0 0.00	0 0.00	15 4.23	281 79.15	59 16.62	355 100.00

Frequency Missing = 1

Table 01.1.9-2 (page 1 of 1)
Distribution of CEA versus SSA-2 at Day 28-predose
(Cross-sectional Analysis Population)

Table of cea_28 by ssa2_28

cea_28(CEA at Day 28) ssa2_28(SSA_2 at Day 28)

Frequency / Percent / Row Pct / Col Pct	0	1	2	3	4	Total
0	0 0.00 0.00 .	0 0.00 0.00 0.00	3 0.91 100.00 2.61	0 0.00 0.00 0.00	0 0.00 0.00 0.00	3 0.91
1	0 0.00 0.00 .	6 1.81 26.09 15.00	10 3.02 43.48 8.70	7 2.11 30.43 4.46	0 0.00 0.00 0.00	23 6.95
2	0 0.00 0.00 .	19 5.74 20.21 47.50	39 11.78 41.49 33.91	31 9.37 32.98 19.75	5 1.51 5.32 26.32	94 28.40
3	0 0.00 0.00 .	14 4.23 8.54 35.00	58 17.52 35.37 50.43	84 25.38 51.22 53.50	8 2.42 4.88 42.11	164 49.55
4	0 0.00 0.00 .	1 0.30 2.13 2.50	5 1.51 10.64 4.35	35 10.57 74.47 22.29	6 1.81 12.77 31.58	47 14.20
Total	0 0.00	40 12.08	115 34.74	157 47.43	19 5.74	331 100.00

Frequency Missing = 25

The Applicant concluded that the SSA scores were noticeably different for patients rated as having no change on the CEA (i.e., investigators report no difference while patients report improvement).

Known-Groups Validity:

Evidence that the instrument can differentiate between clinically distinct groups determines the instrument's known-groups validity. The known groups were defined based on the severity of the facial redness on CEA response on day 28 pre-dose as 0=Clear skin with no signs of erythema; 1=Almost clear of erythema/slight redness; 2=Mild erythema/definite redness; 3=Moderate erythema/marked redness; 4=Severe erythema/fiery redness.

The results indicate that while, the scores (transformed from 0-100) for the SSA were significantly different ($p<0.05$) across the severity groups based on CEA, the mean scores did not increase in monotonic order as expected. See Table 17 below.

Table 17: Known Groups Validity – Among-group Comparison at Day 28 Pre-dose:

Table 17: Known Groups Validity – Among-group Comparison at Day 28 Pre-dose

PROs			
SSA	**N**	**Mean (SD)**	**P-value**
Self-Assessment Facial Redness			
Clear	3	41.70 (14.43)	<0.001
Almost Clear	23	50.00 (22.61)	
Mild	94	55.30 (21.96)	
Moderate	164	63.70(20.22)	
Severe	47	73.40(19.09)	

Reviewer comment: The table above indicates that the overall SSA score is significant among the groups. However, the sponsor has not conducted analysis to demonstrate known groups validity between each pairing of groups (e.g. clear versus almost clear or clear versus mild etc. Transformed scores are difficult to interpret given that raw scores were used for endpoints.

Ability to detect change

The CEA was utilized to compare the pre-determined change groupings (e.g., no change, large positive change, or large negative change) with the SSA. Scores (means and standard deviations) for the SSA were computed for each level of change reported by the CEA and for each level of

severity of erythema reported by the clinician. The groups defined were based on a responder definition (*Change in CEA categories from baseline to Day 28 (pre-dose)*) as follows:

- Marked Improvement ≥2 grade decrease on CEA scores
- Minimal Improvement = 1 grade decrease on CEA scores
- No Change on CEA scores
- Minimal Worsening = 1 grade increase on CEA scores.

Reviewer comment: Sponsor used transformed scores for the SSA analyses. A triangulation method to calculate the minimally important difference (MID) estimates was used. As noted above, transformed scores are difficult to interpret given that raw scores were used for endpoints. The triangulation method used was also uninterpretable. Therefore, these analyses are not presented in this review.

6 INTERPRETATION OF SCORES

DDDP recommended a 2-grade change as a responder, which they would consider as clinically meaningful to patients. The Applicant was able to demonstrate a 2-grade change on the SSA and the CEA. Please see the statistical and clinical reviews for the efficacy data.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Allergan did not perform translations/cultural adaptation of the SSA or the CEA.

8 REVIEW USER MANUAL

The SSA user manual contains information regarding timing of administration of the SSA; instructions for the clinical staff (on procedures such as preparing subjects and training subjects to complete the SSA); subject instruction sheet; and scoring of the SSA.

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/s/

YASMIN A CHOUDHRY
12/02/2016

ELEKTRA J PAPADOPOULOS
12/02/2016

LABEL, LABELING, AND PACKAGING 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:	November 28, 2016
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 208552
Product Name and Strength:	Rhofade (oxymetazoline (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Allergan Inc.
Submission Date:	March 23, 2016
OSE RCM #:	2016-1169
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

Allergan, Inc. submitted NDA 208552 for Rhofade (oxymetazonline [redacted] (b) (4) on March 23, 2016. Thus, the Division of Dermatology and Dental Products (DDDP) requested we evaluate the container labels, carton labeling, and prescribing information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market Rhofade in 30 g and 60 g tubes and pumps. We note that currently marketed products for the treatment of rosacea are available in 30 g, 45 g, and 60 g tubes and 30 g, 50 g, and 55 g pumps. Therefore, we find the proposed 30 g and 60 g package sizes acceptable.

We performed a risk assessment of the proposed container labels, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and other areas of improvement. DMEPA identified the following deficiencies:

Regarding the proposed labels and labeling, we note the following deficiencies:

- The established name is not half the size of the proprietary name as required in CFR 201.10(g)(2).
- It is difficult to distinguish between the tubes and pump presentations.
- The side panel on the container labels is crowded and difficult to read.
- The pump labels and labeling do not instruct the user to discard the first three pumps after priming.

In addition, we note that the applicant submitted the [redacted] (b) (4) However, CMC recommends presenting the strength based on the salt (i.e. oxymetazoline hydrochloride cream, 1%) to be consistent with other oxymetazoline products currently marketed. DMEPA defers to CMC for this determination.

We provide recommendations in Section 4.1 for the container label and carton labeling to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed packaging configurations (i.e (b) (4) mL physician samples, 60 mL and (b) (4) mL bottles) are adequate. However, DMEPA recommends the following be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR ALLERGAN INC.

A. General Comments (All container labels and carton labeling)

1. Ensure the presentation of the established name on all panels is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
2. Revise the dosage form statement from (b) (4) to read "cream".
3. On the principal display panel, increase the prominence of the route of administration statement "For Topical Use Only" by using a larger font size, bold text, and/or a colored font.
4. On the principal display panel, include the statement "Keep Out of Reach of Children" on a single line below the route of administration statement. For example:

   For Topical Use Only

   Keep Out of Reach of Children
5. On the side panel, delete the statement (b) (4) as it has been relocated to the principal display panel (comment A.4.).
6. On the side panel, revise and relocate the information to follow this order:

   Not for oral, ophthalmic, or intravaginal use.

   To open tube (or pump, as applicable):…note: the actual instructions for opening should not use bold font.

   Important: Prime pump before initial use and discard the product from the first three pumps.

   Dosage: … note: the actual dosage instructions should not use bold font.
7. Make sure to include white space between all the sections on the side panel and use a font size that improves legibility.

B. General Comments (All container labels)

1. On the side panel, delete the (b) (4) to reduce clutter and increase legibility of more relevant information to the layperson.

C. General Comments (All carton labeling)

1. On the side panel, relocate the ingredient list statement "Each gram contains…" to below the storage statement.

D. Pump (Container labels and carton labeling)

1. To facilitate differentiation of the tubes from the pumps, include the word "Pump" on the principal display panel of the pump presentations.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rhofade that Allergan Inc. submitted on March 23, 2016.

Table 2. Relevant Product Information for Rhofade	
Initial Approval Date	N/A
Active Ingredient	Oxymetazoline Hydrochloride
Indication	Treatment of persistent facial erythema associated with rosacea in adults
Route of Administration	Topical
Dosage Form	Cream
Strength	1%
Dose and Frequency	Apply a pea-sized amount once daily in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin, avoiding the eyes and lips.
How Supplied	Sample: 3 g tubes Trade: 30 g and 60 g tubes and pumps
Storage	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F)
Container Closure	Laminated tubes; Airless pump polypropylene bottles

APPENDIX B. PREVIOUS DMEPA REVIEWS

N/A

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Allergan labels and labeling submitted by Allergan Inc. on March 23, 2016.

- Container label
- Carton labeling

G.2 Label and Labeling Images

Container Labels (Tube)

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

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/s/

CARLOS M MENA-GRILLASCA
11/28/2016

MISHALE P MISTRY
11/28/2016

Clinical Inspection Summary

Date	October 26, 2016
From	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To	DBRUP\Project Manager\Dawn Williams DBRUP\Medical Officer\Amy Woitach DBRUP\Team Leader\David Kettl Division of Dermatologic and Dental Products
NDA/BLA #	NDA 208552
Applicant	Allergan, Inc.
Drug	Rhofade (oxymetazoline cream, (b) (4) %)
NME (Yes/No)	No
Therapeutic Classification	Standard Review
Proposed Indication(s)	Treatment of persistent facial erythema associated with rosacea in adults
Consultation Request Date	May 9, 2016
Summary Goal Date	October 28, 2016
Action Goal Date	January 6, 2017
PDUFA Date	January 23, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Baumann, Kircik, Moore, and Schleicher were inspected in support of this NDA. The final classification of the inspections of Drs. Baumann, Kircik, and Moore was No Action Indicated (NAI). The final classification of the inspection of Dr. Schleicher was Voluntary Action Indicated (VAI).

Based on the results of the clinical investigator inspections, the studies of Drs. Baumann, Kircik, and Moore appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. Protocol deviations, including the regeneration of missing study documentation and the absence of certain primary efficacy endpoints, were noted during the inspection of Dr. Schleicher. While these protocol deviations do not appear to have had a significant impact on safety or efficacy considerations, the review division may wish to be circumspect in its assessment of the data generated by this site in support of the respective indication.

2. BACKGROUND

The Applicant submitted this NDA to support the use of Rhofade for the treatment of persistent facial erythema associated with rosacea in adults.

Protocols 199201004 and 199201005, both entitled "Efficacy and Safety of Oxymetazoline HCl Cream 1.0% for the Treatment of Persistent Erythema Associated with Rosacea" were inspected in support of this application.

Protocol 199201-004 and 199201-005

The primary objective of these identical studies was to evaluate the efficacy and safety of oxymetazoline HCl cream 1.0% compared with vehicle, applied topically once daily (QD) for 29 days to the face of patients with moderate to severe persistent facial erythema associated with rosacea. These studies randomized subjects in a 1:1:1 ratio to oxymetazoline HCl cream 1.0% or vehicle.

Efficacy was assessed using the investigator's assessment of the patient's overall severity of erythema and using the patient's self-assessment of the overall severity of rosacea facial redness.

Study 199201-004 comprised 440 subjects across 20 centers in the U.S. Study 199201-005 comprised 445 subjects across 24 centers in the U.S. According to the sponsor, these studies demonstrated that oxymetazoline HCl cream 1.0%, applied topically to the face for 29 consecutive days, is safe, well-tolerated, and effective in the treatment of moderate to severe persistent facial erythema associated with rosacea.

Dr. Baumann's site was selected (b) (6) .

Dr. Kircik's site was selected for inspection because of the enrollment of a relatively large number of subjects, response rates for both Rhofade arms much higher than average, and a large treatment effect with 0 successes in the vehicle arm. (b) (6)

Dr. Moore's site was selected for inspection because of the enrollment of a relatively large number of subjects with response rates for both Rhofade and vehicle much higher than average, and a large treatment effect.

Dr. Schleicher's site was selected for inspection because of the very large response rates for the Rhofade treatment arm and a large treatment effect. Nine subjects had protocol violations regarding safety assessments.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
15016/ Baumann, Leslie 4500 Biscayne Blvd., Suites 105 and 101 Miami Beach, FL 33137	199201-005/ 24	21-23 Jun 2016	NAI
14006/ Leon Kircik 1169 Eastern Parkway, Suite 2310 Louisville, KY 40217	199201-004/ 23	20-22 Jun 2016	NAI
14007/ Moore, Angela 711 E. Lamar Blvd., Suite 100 Arlington, TX 76011	199201-004/ 32	21-24 Jun 2016	NAI
15025/ Schleicher, Stephen 20 N Laurel Street, Suite 2A Hazelton, PA 18201	199201-005/ 15	14-28 Jul 2016	VAI

Key to Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Leslie Baumann, M.D.

At this site for Protocol 199201005, 45 subjects were screened, 21 subjects were screen failures, and 24 subjects were enrolled and completed the study.

The study records of all 45 subjects were reviewed for informed consent. Source data was compared with data listings for all 24 enrolled subjects. Records reviewed included, but were not limited to, IRB, sponsor, and monitor correspondence, financial disclosure, inclusion/exclusion criteria, adverse events, electronic patient reported outcomes (ePRO), concomitant medications, and test article accountability,

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Leon Kircik, M.D.

At this site for Protocol 199201-004, 29 subjects were screened, six subjects were screen failures, and 23 subjects were enrolled and completed the study.

All enrolled subjects signed the informed consent form prior to the start of screening procedures. Source documents and Case Report Forms (CRFS) were compared with data listings. The review of the study records of all 23 enrolled subjects included, but was not limited to, financial disclosure, inclusion/exclusion criteria, randomization, the primary efficacy endpoint, test article accountability and storage, adverse events, protocol deviations, and concomitant medications.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Moore, Angela, M.D.

At this site for Protocol 199201-004, 33 subjects were screened, 32 subjects were enrolled, and 30 subjects completed the study.

All enrolled subjects signed the informed consent form prior to the start of screening procedures. Source documents and Case Report Forms (CRFS) were compared with data listings. The study records of 16 subjects were reviewed in depth. The review included, but was not limited to, eligibility criteria, adverse events, IRB communications, and drug accountability.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Stephen Schleicher, M.D.

At this site for Protocol 199201-005, 16 subjects were screened, and 15 subjects were randomized and completed the study.

The study records of all 16 subjects were reviewed. Appropriate informed consent for all subjects was obtained and documented prior to any study-related testing.

Study data (clinical assessment forms/scales) were collected electronically by both clinical investigators and subjects on tablet-style personal computers. Once collected, data was transmitted electronically to a Case Report Form database at the end of a visit and served as the source efficacy assessment data. A program called TrialManager allowed real-time access for monitoring and assessment of study data by the site and the sponsor.

A certified electronic copy of the eCRFs, as provided by a third-party vendor to the site was compared with data contained in the subjects' paper worksheets containing subject visit data (i.e. vital signs, basic physical exam, and check marks indicating completion of protocol-specified procedures such as laboratory testing and efficacy assessment scales. These paper worksheets did not include the values of the scale assessment as they documented the completion of assessments, etc., and included reminders to the subject or clinical investigator to enter data directly into the electronic tablet.

Review of the study records included, but was not limited to, IRB and sponsor communications, financial disclosure forms, protocol deviations, primary and secondary efficacy endpoints, adverse event reporting, concomitant medication logs, and study drug accountability and storage. The site stated that Volume 2 of the regulatory binder which was reported to contain the Delegation of Authority and Signature Sheet, the Monitoring Visit Log, and the Subject Screening and Enrollment Log could not be located. The site said that this log was recreated from available copies and other relevant documents. The log's contents were reviewed with the understanding that these recreated documents do not constitute source documents (see the FDA Form 483 observation below)

A Form FDA 483 was issued at the conclusion of the inspection for inaccurate and/or inadequate records and not conducting the study in accordance with the investigational plan. Observations included, but were not limited, to the following:

Inadequate records including the loss of a regulatory study binder which could not be located during the inspection. The site indicated that this binder contained the Delegation of Authority Log and Signature Sheet, the Monitoring Visit Log, and the Subject Screening and Enrollment Log. These logs were recreated by the study coordinator from duplicate records prior to the inspection. Though these logs were reviewed during the course of the inspection, they do not meet the definition of source documents.

There were missing CRFs for the assessments for Visit 3, Hour 12, for seven subjects. Subjects 3582, 3585, 3586, and 3598 were in the vehicle arm of the study and Subjects 3599, 3600, and 3601 were in the oxymetazoline arm of the study. These visits were indicated as completed on the paper source worksheets which were prospectively completed for assessments that were never actually conducted or recorded in the CRF database. These protocol deviations were reported to the FDA by the sponsor.

Paper source worksheets for Subject 3598 indicate that the Subject Self-Assessment (SSA) and the Clinician Erythema Assessment (CEA) were performed for Visit 3, Hours 3 and 6. However, the electronic case report form database indicated that these visits were not captured at the designated time points. The data on the worksheet were prospectively entered (the subject needed to leave the site during Hours 3 and 6 for an emergent issue) and subsequently not captured by the electronic reporting system. This issue was discovered during a routine monitoring visit.

The primary efficacy assessment is based on both Clinician Erythema Assessment (CEA) and Subject Self-Assessment (SSA) for Rosacea Facial Redness at Hours 3, 6, 9, and 12 on Days 1, 15, and 29 (Visits 2, 3, and 4, respectively) of treatment with the test article. The absence of data for a single interim time point for seven subjects of which three were in the active drug arm would indicate that the missing electronic assessment scores cited in the inspection report had minimal, if any, impact on the primary efficacy assessment.

The study was not conducted in accordance with the protocol in that the temperature monitoring device specified for use in this study was not used, As a result, a monitoring device was used whose expiry date (06/2015) preceded that of disposition of the drug (07/30/2015). There was no indication of temperature excursions.

Dr. Schleicher, in his written response dated July 18, 2016, acknowledged the above protocol deviations, indicating that the unique nature of this study with subject visits extending over 12 hours involving multiple assessments in tight time frames contributed to the noted deviations. In addition, the practice of a newly hired study coordinator in "pre-filling" source documentation worksheets in combination with electronic tablet failures led to some of the deviations noted. Dr. Schleicher has drafted new SOPs and implemented study practices and staff training to prevent such deviations in future studies.

Protocol deviations were noted during this inspection. The recreation of the contents of a missing regulatory binder is not consistent with the precepts of source documentation as promulgated by FDA. Missing primary efficacy endpoint data are also of concern though their impact on the overall primary efficacy assessments was probably mitigated for the reasons noted above.

The protocol deviations noted above do not appear to have had a significant impact on safety or efficacy considerations; however, the review division may wish to be circumspect in its assessment of the data generated by this site in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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/s/

ROY A BLAY
10/26/2016

KASSA AYALEW
10/26/2016