CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208552Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader/Acting Deputy Director Review

Date	January 12, 2017
From	David Kettl, MD, FAAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208552 Related IND: 107983
Applicant	Allergan, Inc.
Date of Submission	March 23, 2016
PDUFA Goal Date	January 23, 2017
Proprietary Name / Non-Proprietary Name	Rhofade (oxymetazoline hydrochloride) cream, 1%
Dosage form(s) / Strength(s)	Topical cream
Applicant Proposed Indication(s)/Population(s)	Topical treatment of persistent facial erythema associated with rosacea in adults
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	RHOFADE cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Rosacea is a chronic condition of uncertain etiology that can affect the facial skin and the eyes of adults. It typically affects the central region of the face e.g., cheeks, nose, chin, and mid forehead. Cutaneous manifestations of rosacea include flushing, persistent (non-transient) erythema, inflammatory papules and pustules, telangiectasia, and sebaceous hyperplasia. The goal of this product is to decrease the persistent (non-transient) erythema that can occur with rosacea.

The conclusion of the clinical review, and that of the entire review team, and concurred by this CDTL review, is that safety and efficacy of Rhofade (oxymetazoline hydrochloride) cream, 1% has been adequately demonstrated by the clinical development program for the topical treatment of persistent facial erythema associated with rosacea in adults. I concur with the recommendations of the multi-disciplinary review team regarding approval of Rhofade (oxymetazoline hydrochloride) cream, 1% for the treatment of persistent (non-transient) erythema of rosacea in adults. An approval action is recommended pending successful completion of ongoing labeling negotiations.

The benefits of Rhofade (oxymetazoline hydrochloride) cream, 1% outweighs the risks when used as recommended in the prescribing information, and this CDTL review concurs with the review team that this application should be approved. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond final agreement of draft. This review will serve as the deputy director signatory review as Dr. Jill Lindstrom is on leave.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Rosacea is a common, chronic cutaneous disorder with clinical symptoms including facial redness, dilated blood vessels on facial skin, papules, pustules, and swelling. The exact cause of rosacea is unknown. There is no curative therapy. Mild disease may not require any treatment beyond cosmetics, but typical treatments include topical and systemic antibiotics, and more severe forms can often require lifelong treatment.	Although the pathophysiology of rosacea remains unknown, the abnormal and persistent dilation of facial blood vessels should be constricted by oxymetazoline resulting in reduced facial erythema.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Mirvaso (brimonidine) gel, 0.33% • However, two currently-marketed products address erythema in their indications: • Noritate ® (metronidazole) Cream, 1% is indicated for "the topical treatment of inflammatory lesions and erythema of rosacea." • Finacea ® (azelaic acid) Gel, 15% is indicated for the "topical treatment of the inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated." • There are also lasers and other devices which are used for the treatment of rosacea and associated erythema	Brimonidine gel, 0.33% is the first product approved in the United States exclusively for the treatment of the erythema of rosacea.
Benefit	• The efficacy and safety of oxymetazoline cream, 1.0% were supported by the two pivotal Phase 3 studies. Both trials were randomized, double-blind, parallel-group, vehicle-controlled, 57-day trials investigating the safety and efficacy of Rhofade cream, 1.0% compared to vehicle cream for the treatment of facial erythema associated with rosacea.	Two adequate and well controlled trials provided adequate evidence of effectiveness in the erythema of rosacea under the proposed conditions of use. The observed treatment effect was small, but was found to be clinically meaningful as well as significantly different from vehicle cream.
Risk	• The proposed size of the safety database appeared adequate for the expected risks. Safety evaluations in the development program were adequate in scope and numbers of subjects, and labeling is sufficient to describe both observed and expected events for the post-marketing environment. • There were no deaths or serious treatment- related TEAEs. In controlled trials, one death occurred in a vehicle-treated subject. The most frequently reported treatment-related TEAEs were application site events. No serious adverse events reported appear to be treatment related. Severe application site reactions (dermatitis,	Based on dermal tolerability assessments and provocative dermal safety studies, oxymetazoline HCl cream 1.0% appears reasonably well tolerated, and the identified risks are acceptable given the demonstrated efficacy. There is extensive experience with over-the-counter intranasal and ophthalmic oxymetazoline products, so concern for this

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	erythema, pain, and pruritus) leading to study discontinuation were reported.	product when used topically for the erythema of rosacea is anticipated to be low in actual use following approval.
Risk Management	• The primary clinical review, as well as this CDTL review, recommends approval of this application. The review team concurs, and there are no issues impacting approval.	Labeling is adequate to describe and inform the risks of this topical therapy. No REMS is recommended by the review team.

2. Background

Allergan, Inc., submitted a 505(b)(1) NDA application on March 23, 2016 for RHOFADE™ [oxymetazoline hydrochloride (HCl)] topical cream, 1.0% and proposes an indication of the "topical treatment of persistent facial erythema associated with rosacea in adults."

Oxymetazoline HCl is a synthetic, direct-acting, imidazoline-type α1A adrenoceptor agonist. Oxymetazoline originally developed by E. Merck in Germany in 1961, was approved by FDA in 1964 as a nasal decongestant Drixine®. The drug is also the active ingredient in several over-the-counter drug products to treat allergic rhinitis and conjunctivitis (e.g., Afrin® nasal spray 0.05%, Dristan, Nasivin, Logicin, Vicks Sinex, and Visine L.R. and OcuClear® ophthalmic solution 0.025%).

FDA recently approved (June 29, 2016) Kovanaze nasal spray for regional dental anesthesia which contains a combination of oxymetazoline hydrochloride and tetracaine hydrochloride.

The proposed product, 0.1% oxymetazoline HCl cream, is being proposed for the treatment of persistent facial erythema associated with rosacea in adults aged 18 years or older. The proposed dosing regimen is once daily (q.d.) in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin.

The original IND application for oxymetazoline HCl cream for the treatment of erythematous rosacea was opened by Vicept Therapeutics, Inc. on March 15, 2010.

In 2011, Allergan, Inc. acquired Vicept Therapeutics, Inc. and IND ownership was transferred from Vicept Therapeutics, Inc. to Allergan, Inc. on July 25, 2011. On July 27, 2011, the Agency and the applicant met for an End-of-Phase 2 (EOP2) meeting, which was requested by Vicept Therapeutics, Inc. on April 7, 2011. During this meeting, the Agency provided comments on the Phase 3 study design and the statistical analysis plan proposed by Vicept Therapeutics, Inc., the proposed nonclinical and CMC plans, and the scales proposed for the Phase 3 program. On May 30, 2012, the applicant submitted a protocol for a non-drug study to validate the Clinician Erythema Assessment (CEA) scale with photonumeric guide. The Agency sent an advice letter regarding this protocol on December 3, 2012.

On December 18, 2013, the Agency and the applicant met for a second EOP2 meeting. The meeting package contained new protocols for two identically-designed Phase 3 trials. The applicant submitted amended protocols for these Phase 3 trials on March 6, 2014, and the Agency sent an advice letter regarding that submission on May 27, 2014. Based on this advice letter, the applicant submitted amended protocols for the Phase 3 trials on July 18, 2014. An advice letter regarding the proposed amendments was sent to the applicant on October 7, 2014.

On October 14, 2015, the applicant and the Agency met for a Pre-NDA meeting. The Agency provided general comments on the content and format of the proposed NDA and how the data should be submitted (data tabulation datasets, data definition files, annotated case report forms, and analysis datasets). During the meeting, the Agency and the applicant discussed the container closure and stability data.

3. Product Quality

The OPQ review team included Drug Substance Reviewer: Jeffrey Medwid, Ph.D., Drug Product Reviewer: Hong Cai, Ph.D., Biopharmaceutics Reviewers: Kelly Kitchens, Ph.D., Process Reviewer: Yaodong Huang, Ph.D., Micro Reviewer: Julie Nemecek, Ph.D., Facility Reviewer: Brian Ryan, Ph.D., Environmental Assessment reviewer: Hong Cai, Ph.D.

The OPQ review team concludes that the applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product and recommends an approval action pending successful completion of labeling.

The facility review team from the Office of Process and Facility (OPF) has issued an "Approval" recommendation for the facilities involved in this application.

The active ingredient used in Rhofade cream, 1% is oxymetazoline hydrochloride, which is highly selective for the α1A adrenoceptor over other α1 adrenoceptors and nonselective for the α2 adrenoceptors. Detailed CMC information on oxymetazoline hydrochloride is provided in DMF # (b) (4) referenced. DMF # (b) (4) has been reviewed (most recently in November, 2015) and found adequate in supporting the use of the drug substance in the drug product of this NDA.

Rhofade will be marketed as a topical white to off-white cream. The cream contains 1.0% (w/w) oxymetazoline HCl which is equivalent to 0.88% (w/w) oxymetazoline free base and will be available in available in tubes and pump bottles.

Rhofade cream in non-metered dose pump is considered a drug-device combination product. The adequacy of the design, function and safety of the pump device including the referred DMF (# (b) (4)) has been reviewed by CDRH reviewer, Lieutenant Commander, Keith Marin who also concludes that there are no issues impacting approval from the device standpoint. Initial priming of the pump is required, and discarding the first three actuations of the pump will be recommended in labeling.

An expiration dating period of 18 months is recommended for the drug product when stored at controlled room temperature.

FACILITY/INSPECTION:

All facilities are **acceptable** after one of the two drug product manufacturing sites, (b) (4) was withdrawn from the NDA. The applicant had proposed two finished drug product manufacturing sites for oxymetazoline hydrochloride cream, 1.0%, namely, (b) (4) and DPT Laboratories (FEI Number: 1628114) located in San Antonio, TX. The (b) (4) site has shown inability to correct previously identified manufacturing issues as shown from repeat 483 observations and particulate matter concerns discovered in the recent inspection. Currently, OPF does not have a high degree of confidence in the (b) (4) site that can reliably and reproducibly manufacture the drug product meeting the quality requirements over the product lifecycle.

APPEARS THIS WAY ON ORIGINAL

The applicant withdrew (b) (4) manufacturing facility from the NDA on November 30, 2016 due to cGMP violations on the site. DPT Laboratories, Ltd., San Antonio-TX, will be used to manufacture the drug product. Although the data related to the drug

product batches manufactured at [redacted] site including batch release and stability have been reviewed, those data are not used to support the approval this NDA.

The OPQ team concluded that [redacted] facility's compliance status will not affect the overall approvability of the NDA. All the current active facilities are deemed acceptable in their identified functions and responsibilities to support approval

QUALITY MICROBIOLOGY

[redacted] Antimicrobial Effectiveness Testing (AET) was performed per USP <51> with samples at 50%, 80%, and 100% of the target concentrations for the [redacted]. The specifications for microbial enumeration and the absence of *E. coli* and *P. aeruginosa* are consistent with those suggested in USP <1111> for a topical product.

ENVIRONMENTAL ASSESSMENT (EA)

A request of categorical exclusion from the requirement to prepare an Environmental Assessment for the drug product in accordance with 21 CFR 25.31(b) was **granted**.

CDRH was consulted to evaluate the applicant's compliance with applicable Quality System Requirements and the review by Bleta Vuniqi concluded that the application is approvable from the perspective of the applicable Quality System Requirements. An analysis [redacted] Regarding the pump, the CDRH review concluded that the device is a low risk device and the applicant is responsible for ensuring the manufacturing is controlled through supplier controls. [redacted] was inspected and not observations were identified; therefore an inspection is not required. Regarding the drug product, an analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted on [redacted] The inspection covered drug GMP and medical device QS requirements and was classified NAI. An inspection is not required because a recent inspection of the firm was acceptable.

There are no outstanding issues related to product quality beyond final agreement on product labeling. There are no post-marketing commitments or post-marketing requirements (PMCs/PMRs) related to product quality.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Cindy Xinguang Li, Ph.D., and concluded that "the toxicity profile of oxymetazoline HCl topical cream has been well characterized by the nonclinical studies conducted by the sponsor."

Her overall nonclinical findings are summarized below:

No evidence of mutagenic or clastogenic potential was identified based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay); and one in vivo genotoxicity test (mouse micronucleus assay at oral doses ≤ 2.5mg/kg/day).

Repeat-dose dermal toxicity studies were conducted in rats for up to 6 months and in minipigs for up to 9 months with oxymetazoline cream. Tail lesions and local toxicities were observed in rats.

The oral Tg.ras H2 mouse assay at doses up to 2.5 mg/kg/day oxymetazoline did not reveal any neoplastic changes. A treatment related increased incidence of non-neoplastic lesions was noted in kidney, brain and mesenteric lymph nodes. The Executive CAC committee review documented that the study was adequate and concurred that the study was negative for drug related neoplasms.

The potential fertility and early embryonic development study toxicity was evaluated after oral administration in rats. Decreased number of corpora lutea and increased post-implantation losses were noted at the high dose of 0.2 mg/kg/day; however, there were no effects on the fertility and mating parameters. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for rat early embryonic development was established at the high dose tested of 0.2 mg/kg/day.

The potential embryo-fetal development toxicity was evaluated after oral administration in rats. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for embryo-fetal development effects was established at the high dose tested of 0.2 mg/kg/day. The Cmax and AUC0-tlast at 0.2 mg/kg/day were 0.541 ng/mL and 3.43 ng.hr/mL on GD day 17, respectively.

The potential embryo-fetal development toxicity was evaluated after oral administration in rabbits. The NOAEL for maternal toxicity was established at the mid-dose of 0.5 mg/kg/day. The NOAEL for embryo-fetal development effects was established at the high dose tested of 1.0 mg/kg/day. The Cmax at 1.0 mg/kg/day was 14.0 ng/mL on GD day 17. The AUC0-24 at 1.0 mg/kg/day was 76.2 ng.hr/mL on GD day 17.

The potential prenatal and postnatal development toxicity was evaluated after oral administration in rats. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for prenatal and postnatal developmental effects was identified at 0.05 mg/kg/day based on increases in pup mortality at 0.2 mg/kg/day and decreased pup weights, observations at necropsy, and delayed sexual maturation at ≥0.1 mg/kg/day.

No safety issues were identified related to any of the product excipients.

Dr. Li's review concludes that there are no significant safety concerns for oxymetazoline HCl cream at the proposed clinical dose based on the nonclinical findings. No nonclinical postmarketing requirements or commitments are recommended for this NDA. Labeling recommendations for the nonclinical sections have been conveyed to the sponsor.

5. Clinical Pharmacology

The clinical pharmacology review was conducted by Yanhui Lu, PhD, with secondary team leader review by Jie Wang, PhD.

Review of the clinical pharmacology program, consisting of four clinical studies that evaluated the PK of oxymetazoline following topical application in subjects with rosacea as well as in vitro studies to evaluate the metabolism and explore the drug interaction potential of oxymetazoline, was adequate to conclude that this application can be recommended for approval. The clinical pharmacology information is supportive of the recommended dosage and administration instructions for Rhofade cream, which describes application of 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.

Dr. Lu's review describes the PK studies as follows:

- **Phase 2 dose-ranging Study 199201-002**. Study 199201-002 provided PK data for oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% administered QD or BID for 28 days in subjects with moderate to severe facial erythema associated with rosacea. This

study provided the PK information for the to-be-marketed formulation of oxymetazoline HCl cream, 1.0%. The dose-response results supported the selection of the 1.0% strength and the QD dosing regimen for Phase 3.

A total of 43 subjects completed the study in the 1.0% QD group. The median weight of study medication applied was 0.3 g per day. Oxymetazoline was measurable in most of the subjects. Following the first dose of oxymetazoline HCl cream 1.0%, the mean (± SD) C_{max} and $AUC_{0\text{-}24hr}$ was 60.5 (± 53.9) pg/mL and 895 (± 798) pg*hr/mL, respectively. After 28 consecutive days of once daily application, the mean (± SD) C_{max} and $AUC_{0\text{-}24hr}$ was 66.4 (± 67.1) pg/mL and 1050 (± 992) pg*hr/mL, respectively. Plasma concentrations of oxymetazoline were below the LLOQ of 10 pg/mL in all subjects on Day 35 (a week after the last dose applied on Day 28). Based on the trough plasma concentrations on Days 2 (24 hours after the dose on Day 1), 14, 28, and 29 (24 hours after the dose on Day 28), the systemic concentrations of oxymetazoline appear to have reached steady state by Day 2.

- **Relative bioavailability Studies V-101-ROSE-201 and V-101-ROSE-205**. Studies V-101-ROSE-201 and V-101-ROSE-205 compared the PK of oxymetazoline HCl cream (0.15% and 0.5%, respectively) to Afrin® nasal spray (0.05%).
- **Dermal tolerability Study 199201-001**. Study 199201-001 provided PK data for oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% applied BID in a split-face manner.

The results of in vitro studies using human liver microsomes showed that oxymetazoline was metabolized into mono-oxygenated and dehydrogenated products of oxymetazoline. The extent of metabolism is limited; and approximately 96% of oxymetazoline remained not metabolized after 120 minute incubation with human liver microsomes.

An exploratory post-hoc analysis did not indicate an increase in oxymetazoline exposure in subjects who experienced co-administration of oral moderate CYP2C19 inhibitors in Study 199201-002.

At the time of, the Applicant requested at the End of Phase 2 meeting whether a thorough QT/QTc (TQT) study for Rhofade could be waived. After review of the available data, the Agency agreed that a TQT study was not needed for Rhofade for the treatment of erythema in patients with rosacea (see Agency Advice Letter dated 03/05/2014).

Dr. Lu's review recommends approval of the application, and no PMC/PMR's are recommended. There are no pending or unresolved issues related to the clinical pharmacology section of the application beyond agreement on recommended labeling.

6. Clinical Microbiology

The applicant asserts no antimicrobial claims, and submitted no clinical microbiology data in this application for review.

7. Clinical/Statistical- Efficacy

The overall clinical development program comprised two identical Phase 3 studies (199201-004 and 199201-005), one Phase 2 dose ranging study (199201-002), nine Phase 1/2 studies, and a long-term safety study (199201-006). The to-be-marketed strength of 1.0% was used in the pivotal Phase 3 clinical studies.

The Phase 2 Study 199201-002 characterized the full pharmacokinetic (PK) profiles of oxymetazoline HCl cream, 1.0% following single dose (Day 1) and multiple dose (Day 28) administrations. The development program evaluated varying oxymetazoline HCl concentrations/strengths ranging from 0.01% to 1.5%.

The efficacy and safety of oxymetazoline cream, 1.0% is supported by the two pivotal Phase 3 studies. Both trials were randomized, double-blind, parallel-group, vehicle-controlled, 57-day trials investigating the safety and efficacy of Rhofade cream, 1.0% compared to vehicle cream for the treatment of facial erythema associated with rosacea. The Phase 2 dose-ranging study provided supportive evidence of effectiveness and supported the selection of oxymetazoline HCl cream, 1.0% daily dosing for Phase 3 studies.

The trials enrolled subjects ≥18 years of age with facial rosacea who had a Clinician Erythema Assessment (CEA) score of ≥3 (moderate to severe erythema) and a Subject Self-Assessment (SSA) score ≥3 (moderate to severe redness).

Dr. Guerra's review reproduces the assessment scales from the trial protocols:

Table 4: Clinician Erythema Assessment (CEA) Scale

Grade	Description
0	Clear skin with no signs of erythema(1)
1	Almost clear of erythema, slight redness
2	Mild erythema, definite redness
3	Moderate erythema, marked redness
4	Severe erythema, fiery redness

Source: Study Protocol
(1) Normal healthy skin color as seen in individuals without rosacea.

Table 5: Subject Self-Assessment (SSA) Scale

Grade	Description
0	No signs of unwanted redness
1	Almost clear of unwanted redness
2	Mild redness
3	Moderate redness
4	Severe redness

Source: Study Protocol

The protocol-specified primary efficacy endpoint was the proportion of subjects with composite success (defined as ≥2-grade reduction in both CEA and SSA) measured at hours 3, 6, 9 and 12 on Day 29. Table 2 presents the results of the primary efficacy endpoint. In both trials, Rhofade cream, 1.0% was statistically superior (p-values <0.001) to vehicle cream.

Rhofade cream, 1.0% was statistically superior (p-values ≤ 0.001) to vehicle cream on the primary efficacy endpoint in both trials. The results from the ITT and PP analyses were similar.

The following table from Dr. Guerra's review captures the primary efficacy results:

Table 2: Composite Success(1) Rates by Hours and Days (ITT, I(2))

	Trial 004	Trial 005

	Rhofade Cream (N=222)	Vehicle Cream (N=218)	P-value[3]	Rhofade Cream (N=224)	Vehicle Cream (N=221)	P-value[3]
Day 29						
Hour 3	12%	6%	<0.001	14%	7%	0.001
Hour 6	16%	8%		13%	5%	
Hour 9	18%	6%		16%	9%	
Hour 12	15%	6%		12%	6%	

Source: Reviewer's Analysis
(1) Composite success is defined as ≥2-grade improvement on both CEA and SSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 20 imputed datasets.
(3) P-value is calculated using imputed data and based on a GEE model with treatment, site and timepoint (hours 3, 6, 9 and 12) as factors in the model.

The primary analysis population specified in the protocol was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol also specified supportive analyses using the per-protocol (PP). The protocol-specified analysis method for the primary efficacy endpoint (i.e., composite success on Day 29) was the Generalized Estimating Equation (GEE) method. For the primary efficacy endpoint, the protocol-specified primary imputation method for the handling of missing data was the multiple imputation (MI) approach. Details of the statistical analyses are further described in Dr. Guerra's review.

For the handling of missing data, the results for the primary efficacy endpoint were similar between the primary imputation method (i.e., multiple imputation using MCMC) and the applicant's sensitivity analyses. Dr. Guerra conducted two additional sensitivity analyses where missing data was imputed as failures and missing data was imputed under the worst cases scenario (i.e., missing data for the RHOFADE arm is imputed as failures and missing data for the vehicle arm is imputed as successes). The results were generally similar to the other imputation methods; however, under the worst case scenario, the results for Trial 005 became marginally non-significant (p-value = 0.066). This was due to a higher amount of missing data in the vehicle arm for Trial 005 compared to Trial 004.

Looking at the scales separately, the CEA reported a slightly higher treatment effect than the SSA. In both trials, the treatment effect was slightly larger in females compared to males. The treatment effect was slightly larger in subjects aged ≥65 years compared to subjects aged 18-64 years in both trials. The treatment effect was larger in non-Caucasians compared to Caucasians in Trial 004. The baseline severity of the majority of subjects was moderate (score of 3) and the results from the primary endpoint (2-grade improvement from baseline in both CEA and SSA) appear to be driven by ≥2-grade improvement on CEA and SSA score of 1 (almost clear).

Additional concerns regarding the scales were presented by the Clinical Outcome Assessment (COA) team review authored by Yasmin Choudhry. COA review found that the SSA was not optimized as an assessment instrument for a variety of reasons. The COA review commented on content validity and test-retest scoring as not optimal, and concordance with the CEA is unknown. Some limitations such as reliability (test-retest) may be explained by the fluctuating nature of erythema in patients with rosacea. Subjects did have difficulty distinguishing between the milder categories. However, the CEA and SSA instruments appear to generally correlate when additional definitions of success were applied and analyzed.

Despite the limitations of the SSA scale identified, Dr. Woitach concluded that the changes seen (and supported by the CEA) are likely to be clinically meaningful to some patients. Of note, a nearly identical scale (PSA) was used in the approval of Mirvaso (brimonidine) gel, 0.33% for the same indication and primary endpoint. This precedent was impactful for consideration of the results from this development program.

Despite the review issues identified during the reviews, and the modest efficacy results, both the clinical and statistical teams concluded that the Applicant has provided substantial evidence of effectiveness required [see 21 CFR 314.126(a)(b)] to support approval. Both the primary clinical and statistical reviews, as well as this CDTL review, concur that efficacy as demonstrated in the phase 3 program is adequate to support a recommendation for approval.

8. Safety

Safety of subjects treated with oxymetazoline HCl cream 1.0% was assessed in trials with treatment periods of 28/ 29 days as well as a long-term 52 week trial which evaluated subjects in sufficient numbers and with sufficient exposures, consistent with the recommendations in the ICH E1A Guideline for Industry. No new safety concerns were identified in the long-term trial.

1412 patients received at least one application of study medication. In the pivotal studies, 489 patients with erythema associated with rosacea were exposed to oxymetazoline HCl cream.

There were no deaths or serious treatment- related TEAEs. In controlled trials, one death occurred in a vehicle-treated subject. The most frequently reported treatment-related TEAEs were application site events. No serious adverse events reported appear to be treatment related. Severe application site reactions (dermatitis, erythema, pain, and pruritus) leading to study discontinuation were reported. Based on dermal tolerability assessments and provocative dermal safety studies, oxymetazoline HCl cream 1.0% appears reasonably tolerated.

Since oxymetazoline acts as an alpha-adrenergic agonist, systemic and ocular hypertension events were specifically considered. In pivotal studies 004 and 005 the preferred term of hypertension was reported for a similar number of subjects in both treatment arms, 2/445 (0.4%) and 3/439 (0.7%) for oxymetazoline HCl cream 1% and vehicle, respectively. In the long-term study 006, 2.5% (11/440) of patients reported adverse events of hypertension over the entire study. Dr. Woitach notes in her review that hypertension is a common disease and it is difficult to assess causality to any of the reported cases. She concludes, "The data to date do not support an increased risk for hypertension related to treatment with oxymetazoline HCl cream 1%."

Intraocular pressure (IOP) was not measured in trials evaluating the safety of oxymetazoline HCl cream 1%. Two Phase 1 trials evaluating a single dose of either 0.15% or 0.5 % oxymetazoline HCl cream evaluated IOP. Pressure measurements were not impacted by treatment.

Despite the lack of specific events related to oxymetazoline, the clinical team recommends that labeling include class warning information on potential risks of systemic and intraocular hypertension.

A single report of a thyroid malignancy was reported in the long-term, open-label trial. Also, there were reports of non-melanoma skin cancer [basal cell (6) and squamous cell (1)]. Dr. Woitach's review of the patient narratives for non-melanoma skin cancers did not identify a relationship between the drug and the adverse event. Although some appeared on the face/ears as would be expected, the lesions occurred outside of the recommended area of application. Dr. Woitach notes that there is no mechanistic reason to suspect that exposure to oxymetazoline cream contributed to development to any of these malignancies. In the development program, the applicant was granted a waiver request for conduct of a dermal carcinogenicity study. Given the context of the indication, and the history of treatment with other oxymetazoline products, labeling for these cancer related events is not recommended.

Laboratory evaluations (i.e., hematology, chemistry, and urinalysis) were conducted in Study 199201-002. Laboratory assessments were not deemed necessary in the pivotal studies and Study 006 because, in Study 002, changes from baseline were small across each evaluated parameter and were not considered to be clinically relevant.

The Agency determined that a tQT study was not needed based on a review of Phase 2 trial data. Electrocardiograms (ECGs) were performed in Study 002. ECGs were not deemed necessary as part of the safety evaluation in the Pivotal Studies (004 and 005) and Study 006, because the results from ECG evaluations in Study 002 concluded that topical oxymetazoline HCl cream 1.5%, 1.0%, and 0.5% administered QD or BID for 28 consecutive days did not cause clinically significant ECG changes.

Dermal safety studies are acceptable to inform product labeling. Irritation was noted to be mild in severity and local adverse events were prospectively assessed in the Phase 3 program. The applicant concluded that there was no evidence of sensitization for any of the test products. No evidence of phototoxicity or photoallergenicity was identified. No labeling for photo-protection is recommended at this time.

Oxymetazoline HCl cream 1.0% is not expected to have any potential for abuse or dependence.

In conclusion, safety evaluation in the development program was adequate in scope and numbers of subjects, and labeling is sufficient to describe both observed and expected events for the post-marketing environment. As noted above, there is extensive experience with over-the-counter intranasal and ophthalmic oxymetazoline products, so concern for this product when used topically for the erythema of rosacea is anticipated to be low in actual use following approval.

9. Advisory Committee Meeting

No Advisory Committee meeting was conducted for this application. The review team determined early in the application review cycle that this new formulation for topical oxymetazoline cream presented no novel or complex regulatory issues that required the input of an advisory committee. Efficacy assessments had adequate precedence in other applications.

10. Pediatrics

Rosacea occurs primarily in adults, although it has been infrequently reported in children. The Agency has agreed to the Applicant's full waiver request of the requirement to conduct studies in pediatric patients from 0 to 17 years of age (see Advice Letter dated 07/18/2014).

The waiver was granted based on the justification that:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (Section 505B(a)(4)(A)(i) of the Act).

The review team concurred that the erythema of rosacea, as well as rosacea itself, does not occur with sufficient frequency to be studied in any pediatric population. The prevalence rate in children 0 to 17 years of age was determined to be (b) (4)%.

The recent approval for the same indication [NDA 204708 for Mirvaso (brimonidine) topical gel, 0.33% on 23 August 2013], was also granted a full waiver of the pediatric study requirement because the Agency determined "necessary studies are impossible or highly impracticable because there are too few children with this condition to study."

The Pediatric Review Committee provided concurrence with the full waiver request at their meeting of January 11, 2017.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

GMP inspections are pending an "Acceptable" determination from the Office of Compliance for the facilities inspections as of the date of this CDTL review.

The Division of Scientific Investigators (DSI) was consulted to review study sites related to the conduct of clinical trials. Four sites were chosen for inspection based on centers demonstrating a higher or large treatment effect, reported protocol violations or financial

conflicts of interest. Three of the four study site inspections received NAI, and one had minor issues that warranted a VAI recommendation. No significant irregularities were noted by the review team during the review.

There are no outstanding regulatory issues that impact the approval of this application.

12. Labeling

The trade name of "Rhofade" has been accepted by Office of Medication Error Prevention and Risk Management (OMEPRM/DMEPA).

Review of the proposed label submitted by the applicant was based on evaluation of the clinical trials for the NDA as well as DMEPA, DRISK, and OPDP consultative reviews.

Professional labeling conforms to the standards of the Physician Labeling Rule. Patient labeling, comprised of Patient Information and Instructions for Use, contains text and diagrams to inform patients about safe use of the product. PLLR compliance in the label has been adequately addressed.

Labeling is adequate to communicate necessary safety information to prescribers. Final agreement on Agency proposed labeling, including carton/container labeling, is pending as of the date of this CDTL review.

The major labeling issue relates to the type and degree of data to be presented in the Clinical Section 14. The applicant is proposing to include (b) (4)

(b) (4)

(b) (4)

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The review team concluded that a REMS is neither required nor recommended for this product. Labeling is adequate to inform prescribers and patients of expected adverse events and risks.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

None.

14. Recommended Comments to the Applicant

There are no comments to be conveyed to the applicant beyond agreement of final labeling. Labeling negotiations are ongoing with the applicant as of the date of this review, but there are only minor differences to be resolved as of the date of this CDTL review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID L KETTL
01/18/2017