CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204708Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 21st, 2013
From	Susan J. Walker, MD, FAAD
Subject	Division Director Summary Review
NDA #	204708
Applicant Name	Galderma
Date of Submission	October 26th, 2012
PDUFA Goal Date	August 25th, 2013
Proprietary Name / Established (USAN) Name	Mirvaso/Brimonidine
Dosage Forms / Strength	Gel/ 0.33%
Proposed Indication(s)	Topical treatment of persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older.
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review,TL	Brenda Carr, M.D, Jill Lindstrom, M.D.
Statistical Review, TL	Matthew Guerra, Ph.D, Mohamed Alosh, Ph.D.
Pharmacology Toxicology Review,TL	Jianyong Wang, Ph.D, Barbara Hill, Ph.D.
CMC Review, TL	Hitesh Shroff, Ph.D, Moo Jong Rhee, Ph.D.
Clinical Pharmacology Review. TL	An-Chi Lu, M.S., Pharm.D., Doan Tran, Ph.D.
Cross Discipline Team Leader	Jill Lindstrom, M.D.

OND=Office of New Drugs
TL=Team Leader
CMC-Chemistry Manufacturing and Controls
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This 505(b) (2) application proposes the use of brimonidine topical gel, 0.33%, for the treatment of the persistent facial erythema of rosacea in adults. The drug substance is an alpha adrenergic receptor agonist and this is a novel substance for dermatologic topical application. The review team is aligned in recommendations for approval of this application and I concur with the discipline recommendations. This review will briefly summarize the major issues pertinent to approvability of this application by referencing the individual discipline summaries.

2. Background

Rosacea is a chronic cutaneous condition that predominantly affects the central region of the face e.g. cheeks, nose, chin, and mid forehead. It may be characterized by flushing, persistent erythema, telangiectasia, and inflammatory papules. This application proposes treatment of only the erythema of rosacea, and does not claim efficacy for treatment of papules or telangiectasia. While ocular involvement may occur, this was not a focus of this application.

Alpha-2 adrenergic agonists are most commonly use in the treatment of systemic hypertension, and can also be used to decrease intraocular pressure. This application presents a novel use of an alpha adrenergic agonist for the treatment of erythema. I concur with the recommendation by Dr. Carr, the clinical reviewer, that the indication be reserved to the "persistent erythema of rosacea".

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

As summarized by Dr. Wang, the sponsor proposed to rely upon the Agency's finding of safety for the approved listed drug ALPHAGAN® ophthalmic solution, 0.2% to support some

nonclinical portions of this 505(b) (2) application. The systemic exposure of once daily maximum clinical use of MIRVASO Gel, 0.5% ((b) (4) applied to the entire face) was less than that of brimonidine tartrate ophthalmic solution 0.2% at its approved dose of 1 drop into each eye TID.

In addition to relying upon the Agency's finding of safety for the listed drug, including information regarding genetic toxicity, reproductive toxicity, and oral carcinogenicity, the sponsor also conducted pivotal repeat dose dermal toxicity studies in rats and minipigs, a photo-carcinogenicity study in hairless mice, a dermal rat carcinogenicity study, and several special toxicology studies.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant is seeking approval of Mirvaso (brimonidine) gel, 0.33% for the treatment of facial erythema of rosacea in adults 18 years of age or older.

Efficacy findings from two pivotal trials (Studies 18140 and 18141) established that MIRVASO topical gel was superior to vehicle gel in the treatment of persistent facial erythema of rosacea in adults 18 years of age or older. Clinical evaluations included both a physician's assessment and a patient assessment, and demonstration of efficacy required "success" on both evaluations.

MIRVASO Gel was evaluated for the treatment of moderate to severe, persistent (nontransient) facial erythema of rosacea in two randomized, double-blind, vehicle-controlled clinical trials, which were identical in design. The trials were conducted in 553 subjects aged 18 years and older who were treated once daily for 4 weeks with either MIRVASO Gel or vehicle. Overall, 99% of subjects were Caucasian and 76% were female. Baseline disease severity was graded using a 5-point Clinical Erythema Assessment (CEA) scale and a 5-point Patient Self Assessment (PSA) scale, on which subjects scored either "moderate" or "severe" on both scales.

The primary efficacy endpoint in both pivotal trials was 2-grade Composite Success, defined as the proportion of subjects with a 2-grade improvement on both CEA and PSA measured at hours 3, 6, 9, and 12 on Day 29. Table 2 presents the efficacy results. In addition to Day 29, efficacy was evaluated on Day 15 and Day 1, and the results are presented in Figures 1 and 2 for Studies 1 and 2, respectively.

Table 2: Summary of 2-grade Composite Success on Day 29

Success	Study 1		Study 2	
	MIRVASO Gel (N=129)	**Vehicle Gel (N=131)**	**MIRVASO Gel (N=148)**	**Vehicle Gel (N=145)**
Hour 3	31%	11%	25%	9%
Hour 6	30%	10%	25%	9%
Hour 9	26%	10%	18%	11%
Hour 12	23%	9%	22%	10%

2-grade Composite Success: 2-grade improvement on CEA and 2-grade improvement on PSA.

Figure 1: 2-grade Composite Success by Hour and Day for Study 1

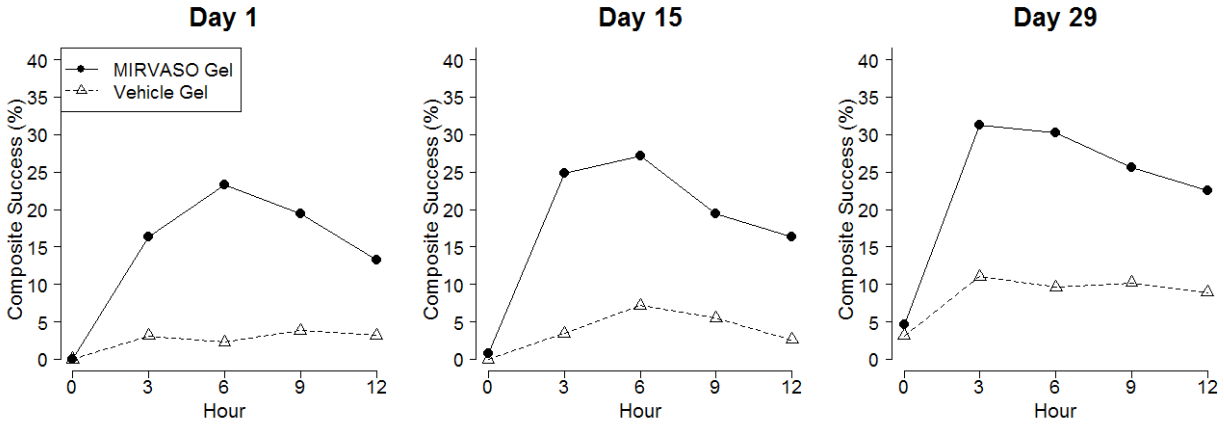
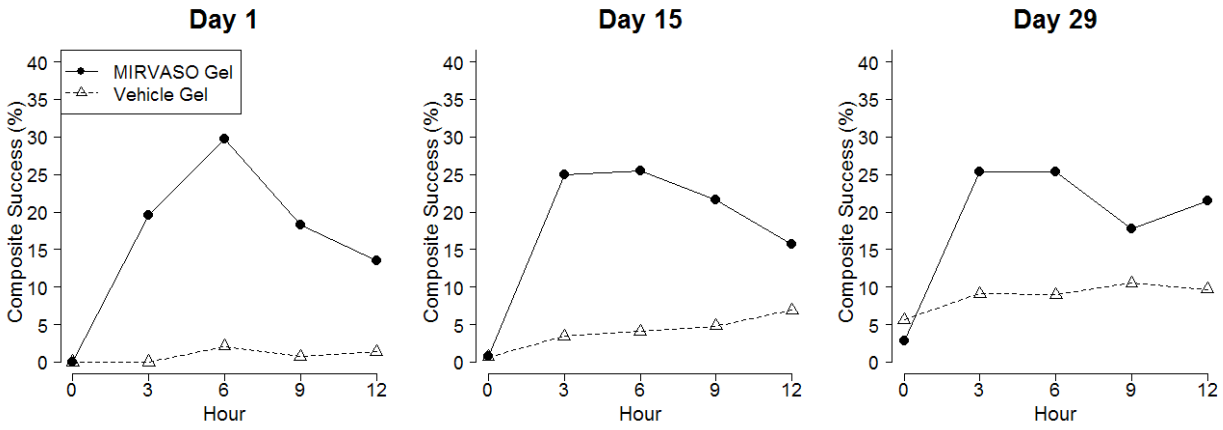


Figure 2: 2-grade Composite Success by Hour and Day for Study 2



8. Safety

A total of 2174 subjects were evaluated in the clinical development program. Of these, 1619 subjects were exposed to brimonidine tartrate gel; with 1210 subjects exposed to brimonidine 0.33% gel QD. Mean duration of treatment was approximately 28 days, and the mean daily amount of gel exposure was 0.8grams. Adverse reactions that occurred in at least 1% of treated subjects and for which the rate exceeded the vehicle by more than 1% included erythema and flushing. Some subjects in the clinical trials discontinued use of MIRVASO Gel because of erythema or flushing. The effect of MIRVASO Gel may begin to diminish hours after application. For some subjects in the clinical trials, erythema was reported to return worse compared to the severity at baseline

There were no systemic adverse events in the clinical trial subjects that were attributed to the pharmacology of the drug product.

Two young children of a subject in a clinical trial experienced serious adverse reactions following accidental ingestion of MIRVASO Gel. Adverse reactions experienced by one or both children included lethargy, respiratory distress with apneic episodes (requiring intubation), sinus bradycardia, confusion, psychomotor hyperactivity, and diaphoresis. Both children were hospitalized overnight and discharged the following day without sequelae. MIRAVASO gel includes a Patient Package Insert to address the product risks, and the product, as with all medications, should be kept out of the reach of children. The approved product will include a child-resistant container closure system to manage the risk of unintended exposure to brimonidine gel.

Long term safety was evaluated in 333 subjects for > 180 days and 276 subjects for > 365 days. Mean duration of treatment was approximately 278 days and mean daily amount of gel exposure was 0.5 grams.

An open-label study of MIRVASO Gel applied once daily for up to one year was conducted in subjects with persistent (nontransient) facial erythema of rosacea. Subjects were allowed to use other rosacea therapies. A total of 276 subjects applied MIRVASO Gel for at least one year.

The most common adverse events (≥ 4% of subjects) for the entire study were flushing (10%), erythema (8%), rosacea (5%), nasopharyngitis (5%), skin burning sensation (4%), increased intraocular pressure (4%), and headache (4%).

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Rosacea is a condition that affects adult patients. Pediatric study requirements for this application are waived because necessary studies are impossible or highly impracticable because there are too few children with this condition to study.

11. Other Relevant Regulatory Issues

There are no other unresolved regulatory issues.

12. Labeling

- Proprietary name of MIRVASO has been granted.
- Physician labeling has been discussed on concluded.
- Carton and immediate container labels have been discussed and concluded
- Patient labeling has been discussed and concluded

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – This application will be approved.

- Risk Benefit Assessment – This product presents a novel therapeutic treatment for the persistent erythema of rosacea. The benefits of the product outweigh the risks to the patient.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None.

- Recommendation for other Postmarketing Requirements and Commitments – None.

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

/s/

SUSAN J WALKER
08/21/2013