CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204708Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	20 August 2013
From	Jill Lindstrom, MD
Subject	Cross-Discipline Team Leader Review
NDA #	204708
Applicant	Galderma Research and Development, Inc.
Date of Submission	25 October 2012
PDUFA Goal Date	25 August 2012
Proposed Proprietary Name	MIRVASO topical gel
Established (USAN) names	brimonidine
Dosage forms / Strength	Gel, 0.33%
Proposed Indication	Treatment of facial erythema of rosacea in adults 18 years of age or older
Recommended:	*Approval*

1. Introduction

MIRVASO (brimonidine) topical gel, 0.033% is a topical drug product for which the applicant seeks approval under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act for the topical treatment of facial erythema of rosacea in adults 18 years of age and older. The active ingredient, brimonidine, is marketed in the United States for the reduction of ocular hypertension. This memo will summarize the findings of the multi-disciplinary review team and provide the rational for my recommended action.

2. Background

Rosacea is a chronic condition of uncertain etiology that can affect the facial skin and the eyes of adults. Cutaneous manifestations of rosacea include flushing, persistent (non-transient) erythema, inflammatory papules and pustules, telangiectases, and sebaceous hyperplasia. The applicant developed their product to address the persistent (non-transient) erythema that can occur with rosacea.

The therapeutic armamentarium for the treatment of rosacea includes approved and unapproved drug products as well as devices such as lasers and intense pulsed light. Approved products indicated for the treatment of the inflammatory papules and pustules of rosacea include topical drugs such as metronidazole and finasteride, and oral doxycycline.

The active ingredient, brimonidine, can be described as the moiety (brimonidine) or the salt (brimonidine tartrate). In this drug product, the concentration of the moiety (brimonidine) is 0.33% and of the salt (brimonidine tartrate) is 0.5%. The application generally refers to the salt, but in order to conform with the USP naming policy for salt substances which went into effect on 1 May 2013, the labeling will refer to the moiety. Both designations are used in this review.

3. CMC/Device

The drug substance, brimonidine tartrate, is a white to yellowish powder that is freely soluble in water. It has a molecular formula of C11H10BrN5·C4H6O6 and a molecular weight of 442.2 (b) (4) g/mol. It acts as a selective alpha$_2$-adrenergic receptor agonist and it has been marketed in the US as an ophthalmic solution for treatment of glaucoma since 1996.

The drug product, MIRVASO (brimonidine) fopical gel, 0.33%, is a white to light yellow opaque aqueous gel. Each gram of the gel contains 5mg of brimonidine tartrate (salt) or 3.3mg of brimonidine. The composition is described in the following table:

Ingredient	Function	% w/w
Brimonidine tartrate	Drug substance	0.5
(b) (4)		(b) (4)
Methylparaben		
Phenoxyethanol		
Glycerin		
Titanium dioxide		
Propylene glycol		
Sodium hydroxide		
Purified water		

Source: adapted from NDA 204708 section 2.3.P.2.1.1

There are no novel excipients in the formulation; all of the excipients are USP/NF grade. The product is an aqueous gel, and contains methylparaben and phenoxyethanol as preservatives to prevent microbial growth.

The drug product is packaged into 30g and 45g (b) (4) laminate tubes with (b) (4) "push an turn" child-resistant caps. (b) (4) Stability data support an expiry of 24 months.

Facilities inspections for the drug substance and drug product were acceptable.

The CMC reviewer, Dr. Hitesh Shroff, concluded that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product, and did not recommend any postmarketing commitments. He identified unresolved labeling issues (pending at the time of close of this review) which would preclude a recommendation for Approval.

4. Nonclinical Pharmacology/Toxicology

The applicant conducted repeat dose dermal toxicity studies in rats and minipigs, a photo-carcinogenicity study in hairless mice, a dermal rat carcinogenicity study, and irritancy and sensitization studies. Findings included reduction in body weight gain in rodents. Interestingly, in the photocarcinogenicity study, there was a dose-related reduction in UV-related tumor response seen with brimonidine compared to vehicle and untreated groups.

The applicant is relying on the Agency's previous finding of safety for ALPHAGAN ophthalmic solution, 0.2% to supply the genetic toxicity, reproductive toxicity, and oral carcinogenicity safety data needs.

The relevant information has been proposed for inclusion in labeling, negotiations on which are pending at the time of close of this review.

The reader is referred to the comprehensive review by Dr. Jianyong Wang for a full discussion of the nonclinical pharmacology/toxicology data. Dr. Wang did not recommend further nonclinical studies or phase 4 commitments, and recommended an Approval action from a pharmacological/toxicological perspective pending resolution of labeling.

5. Clinical Pharmacology/Biopharmaceutics

MIRVASO (brimonidine) Topical Gel, 0.33% is a topical product for the treatment of the persistent erythema of rosacea in adults. It is applied once daily to the involved skin of the face.

The applicant conducted Study 18143, a multiple-dose, cross-over design trial of MIRVASO topical gel and the listed drug in subjects with rosacea, to assess comparative bioavailability, pharmacokinetics and systemic exposure under maximum usage conditions. Ninety-six evaluable subjects with moderate to severe erythema of rosacea were treated with the listed drug (brimonidine ophthalmic solution 0.2% TID) for one day, underwent a 2-day washout period, and were subsequently treated with brimonidine tartrate topical gel (0.07% BID, 0.18% QD or BID, or 0.50% QD) for 29 days. The C_{max} and $AUC_{0\text{-}24hr}$ for brimonidine tartrate topical gel, 0.5% were less than for brimonidine ophthalmic solution, allowing Dr. Lu to conclude that the systemic exposure from brimonidine tartrate topical gel, 0.5% applied under maximal use conditions is less than that from brimonidine ophthalmic solution, 0.2% TID use as labeled; this supports the clinical bridge.

The applicant conducted a thorough QT/QTc study using a single supratherapeutic dose (2 drops in each eye) of brimonidine ophthalmic solution, 0.2%. No significant effect on repolarization was identified.

Dr. An-Chi Lu found the application acceptable from a clinical pharmacology perspective, pending resolution of labeling negotiations.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

To establish the effectiveness of their product, the applicant submitted data from two pivotal trials, Study 18140 and Study 18141. These two studies, identical in design, were randomized, double-blind, vehicle-controlled, and parallel-group with two arms. The trials enrolled adult subjects with moderate or severe non-transient facial erythema of rosacea, as assessed by the Clinician Erythema Assessment (CEA) scale and the Patient('s) Self Assessment (PSA) scale. Subjects applied study drug once daily for 29 days. Efficacy assessments were performed at hours 3, 6, 9 and 12 on days 1, 15 and 29. The primary efficacy endpoints were a 2-grade Composite Success at Hours 3, 6, 9, and 12, defined as a 2-grade improvement on both CEA and PSA at each time point, on Day 29, then on Day 15, and then on Day 1.

The applicant was granted a Special Protocol Assessment (SPA), and an Agreement letter was issued on 30 March 2011. Agreements included:

- General study design
- Dose regimen: 0.5% brimonidine tartrate gel or vehicle gel, applied once daily for 29 days
- Disease severity proposed for study: adults with facial rosacea and a CEA and PSA score of $\geq$3 at baseline and with no more than 3 inflammatory lesions
- Subject assessment on days 1, 15, 29, week 6 and week 8
- Primary endpoint: composite success at hours 3, 6, 9 and 12 on Days 29, 15 and 1, where success is defined as a 2-grade improvement on both CEA and PSA at each time point
- Primary analysis population: Intent to Treat (ITT) population, defined as all randomized subjects to whom study drug is administered
- Laboratory assessments: blood chemistry, hematology and urinalysis at screening, day 29, and as needed.

The results of the primary efficacy endpoint are presented in the following table:

	Study 18140			Study 18141		
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**p-value**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**	**p-value**
Day 29						
Hour 3	31.2%	11.0%	<0.001	25.3%	9.1%	<0.001
Hour 6	30.2%	9.6%		25.3%	9.0%	
Hour 9	25.6%	10.2%		17.7%	10.5%	
Hour 12	22.5%	8.9%		21.5%	9.7%	
Day 15						
Hour 3	24.8%	3.4%	<0.001	25.0%	3.4%	<0.001
Hour 6	27.1%	7.2%		25.5%	4.1%	
Hour 9	19.4%	5.5%		21.6%	4.8%	
Hour 12	16.3%	2.6%		15.7%	6.9%	
Day 1						
Hour 3	16.3%	3.1%	<0.001	19.6%	0%	<0.001
Hour 6	23.3%	2.3%		29.7%	2.1%	
Hour 9	19.4%	3.8%		18.2%	0.7%	
Hour 12	13.2%	3.2%		13.5%	1.4%	

Source: adapted from Statistical Review and Evaluation NDA 204708; Matthew Guerra, PhD, archived 11.6.2013, p 3.

In Study 18140 and Study 18141, MIRVASO topical gel was superior to vehicle on days 29, 15 and 1.

The reader is referred to the biostatistical and clinical reviews by Matthew Guerra, PhD, and Brenda Carr, MD, respectively for detailed review of the pivotal trials and additional analyses, including post hoc explorations of the data and sensitivity analyses.

I concur with Drs. Guerra and Carr that the clinical trial data support a determination of efficacy.

8. Safety

Eight hundred and thirty-three subjects with rosacea were exposed to brimonidine gel, 0.33%, during the development program. Of these, 277 subjects were exposed to MIRVASO topical gel in the pivotal trials, Study 18140 and Study 18141. In the open-label extension study, 18142, 333 subjects were exposed to MIRVASO Topical Gel for at least 6 months, and 276 of these subjects for at least one year.

One death was reported during the development program: a 65-year old former smoker died of complications of squamous cell carcinoma of the lung. The investigator considered this serious adverse event to be unrelated to study drug, with which I agree. Nineteen subjects reported serious adverse events occurring to themselves (one subject reported SAEs involving

her two children, discussed separately). None of these were judged by the investigators to be related to MIRVASO topical gel, although the SAE for one subject (hypotension) was considered related to brimonidine ophthalmic solution.

One subject in Study 18140 reported SAEs that occurred in her two children, aged 3 years and 18 months, who reportedly used the subject's study drug as toothpaste. Hyperactivity, irregular heartbeat, and lethargy were reported for the 3 year old, and lethargy and respiratory distress for the 18 month old child. Both children were hospitalized overnight, and released the following day without apparent complication.

Adverse events were reported more frequently for subjects receiving active than vehicle: 33% versus 28% in the pooled safety population from controlled trials. The most common adverse events occurring at a frequency of >1% in subjects treated with active include erythema, flushing, and skin burning sensation. Active assessment for ocular pressure (selected studies) and heart rate did not reveal a safety signal.

Laboratory assessments (chemistries, complete blood count, urinalysis) were conducted in the pivotal trials and the open label study (18140, 18141, 18142). No significant trend or safety signals were identified.

A special safety concern is the risk of ingestion-type medication errors, as occurred in the children of a subject in Study 18140. The applicant addressed this risk through professional, patient, and carton and container labeling, as well as by the implementation of a child-proof container closure for the trade size tubes.

The reader is referred to the clinical review by Dr. Brenda Carr for a full discussion of the safety database.

9. Advisory Committee Meeting

Not applicable, as no advisory committee meeting was held.

10. Pediatrics

Rosacea occurs primarily in adults, although it has been reported in children. The applicant requested a waiver for all pediatric age groups on the grounds that pediatric studies would be impossible or highly impracticable because there are too few children with the disease/condition to study. The Pediatric Review Committee (PeRC) agreed with the Division's recommendation to grant a complete pediatric waiver for ages 0 to 16 because rosacea is rare in children.

11. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.

12. Labeling

All components of labeling were reviewed. Labeling negotiations with the applicant are ongoing at the time of close of this review.

Carlos Mena-Grillasca, RPh, of Division of Medication Error Prevention and Analysis found the proposed proprietary name, MIRVASO, to be acceptable.

The applicant proposed, (b) (4) as the established pharmacologic class (EPC) for MIRVASO topical gel. However, "alpha adrenergic agonist" is the EPC for the listed drug, brimonidine ophthalmic solution. The pharmacology-toxicology reviewer recommended that the EPC for MIRVASO be "alpha adrenergic agonist," consistent with the listed drug.

The clinical reviewer proposed modification of the indication to specify that the product is intended to treat the persistent (non-transient) erythema of rosacea, to distinguish from the transient flushing that can also occur with the condition.

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, including operation of the child-resistant container closure.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Approval*.

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 204708 MIRVASO (brimonidine) topical gel, 0.33% for the treatment of persistent (non-transient) erythema of rosacea in adults.

Risk-benefit assessment: The applicant established the efficacy and safety of MIRVASO topical gel in the treatment of persistent erythema of rosacea in adults in two adequate and well-controlled trials, and provided sufficient information in their application to support product labeling. The efficacy of the product for the indication, for which there are no other medical treatment options, justifies the modest risks, the most significant of which appears to be ingestion-type medication errors.

Recommended postmarketing Risk Evaluation and Management Strategies: None. Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not recommended.

Recommended postmarketing requirements (PMR) and commitments (PMC): None. No postmarketing requirements or commitments are recommended.

Recommended comments to applicant: none

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/s/

JILL A LINDSTROM
08/20/2013