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APPLICATION NUMBER:

206255Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	19 December 2014
From	Jill Lindstrom, MD
Subject	(acting) Deputy Division Director Summary Review
NDA #	206255
Applicant Name	Galderma Research and Development, LLC
Date of Submission	24 December 2013
PDUFA Goal Date	
Proprietary Name	Soolantra
Established (USAN) Name	ivermectin
Dosage Forms	cream
Strength	1.0%
Proposed Indication(s)	the topical treatment of the inflammatory lesions of rosacea
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jane Liedtka, MD
Statistical Review	Matthew Guerra, PhD
Pharmacology Toxicology Review	Jianyong Wang, PhD
CMC Review	Raymond Frankewich, PhD
CMC Microbiology Review	Vinayak Pawar, PhD
CMC Biopharmacology	Kelly Kitchens, PhD
Clinical Pharmacology Review	Chinmay Shukla, PhD
DPP	Tara Turner, PharmD, MPH
OSE/DMEPA	Carlos Mena-Grillasca, RPh
PLT	Nathan Caulk, MS BSN RN
NDMAB	Christina Capacci-Daniel
DGCPC	Roy Blay, PhD
Other	

OND=Office of New Drugs
DPP=Division of Professional Promotion (formerly part of Division of Drug Marketing, Advertising and Communication)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
PLT=Patien Labeling Team (formerly part of DRISK)
NDMAB=New Drug Manufacturing Assessment Branch
DGCPC=Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigations)

1. Introduction

Soolantra (ivermectin) cream, 1.0%, 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 treatment of the inflammatory lesions of rosacea in adults 18 years of age and older. The active ingredient, ivermectin, is marketed in the United States as a 3mg tablet for the treatment of strogyloidiasis and onchocerciasis (Stromectol, Merck), a 0.5% lotion for the treatment of head lice infestation (SKLICE, Topaz), as well as in a variety of formulations for veterinary use. The applicant submitted published literature to describe the peri and postnatal toxicity of ivermectin, but owns the remainder of the data provided to support the safety and efficacy of Soolantra. This memo, which serves as my deputy division director review as well as the cross-discipline team leader review (a role which I fulfilled during the review cycle) will summarize the findings of the multi-disciplinary review team and provide the rationale for my decision.

2. Background

Rosacea is a chronic inflammatory disease of uncertain pathogenesis that primarily affects the facial skin of adults. Rosacea can be classified into four subtypes (with overlap): erythematotelangiectatic, papulopustular, rhinophymatous, and ocular. Clinical manifestations include erythema, flushing, telangiectases, inflammatory papules and pustules, sebaceous hypertrophy and cutaneous stinging and burning. The therapeutic armamentarium for rosacea includes topical metronidazole, topical azelaic acid, and oral doxycycline (for the treatment of inflammatory lesions), and topical brimonidine and laser treatment (for the treatment of erythema).

Ivermectin, a member of the avermectin class, is derived from fermentation of a soil-dwelling actinomycete, *Streptomyces avermitilis*. In invertebrates such as *Strongyloides stercoralis, Oncocerca volvulus* and *Pediculus humanus capitis*, ivermectin binds to glutamate-gated chloride channels in nerve and muscle cells causing cell hyperpolarization with resultant paralysis and death. However, the mechanism of action of ivermectin in the treatment of the inflammatory lesions rosacea is unknown.

3. CMC/Device

The drug substance, ivermectin, is a mixture of two components: B_{1a} and B_{1b}. The molecular formulas (and weights) of the components are $C_{48}H_{74}O_{14}$ (875.1) and $C_{47}H_{72}O_{14}$ (861.1), respectively. Physically, ivermectin is a white to yellowish-white powder that is soluble in methanol or acetone but not in water.

The drug product, Soolantra (ivermectin) cream, is off-white to pale yellow in color and contains 1.0% (10 mg/gm) of ivermectin. The composition is described in the following table:

Ingredient	Function	% w/w
Ivermectin	Drug Substance	1.0
Glycerin	[redacted]	[redacted]
Isopropyl palmitate		
Cetyl alcohol		
Polyoxyl 20 cetostearyl ether		
Stearyl alcohol		
Oleyl alcohol		
Propylene glycol		
Sorbitan monostearate		
Phenoxyethanol		
Dimethicone [redacted]		
Carbomer copolymer (type B)		
Methylparaben		
Propylparaben		
Citric acid monohydrate		
Edetate disodium		
Sodium hydroxide [redacted]		
[redacted]		
Purified Water		

Source: adapted from NDA 206255 section 2.3.P p6.

There are no novel excipients. The product, which contains water, is formulated with phenoxyethanol, methylparaben, and propylparaben [redacted] Microbial limits test is included in the finished product specifications.

The formulation proposed for marketing is identical to the formulation used in the Phase 3 trials; however, the manufacturing process differs. The changes, instituted to ensure [redacted] represent Level 2 change per SUPAC—SS. The applicant performed in vitro release testint (IVRT) to bridge between the two processes. The biopharmaceutics reviewer, Dr. Kelly Kitchens, found that the applicant's IVRT was validated and that data from this testing demonstrated the sameness of product manufactured with the different processes, regardless of batch age.

The dosage form, a cream, is [redacted] emulsion. [redacted] were seen by microscopy [redacted] Because of the lack of information provided by the applicant regarding the characteristics of [redacted] and the uncertainty about the impact of the [redacted] on drug delivery, the applicant was requested to include an in vitro release test (IVRT) in the drug product release and stability specifications as a control for these [redacted].

The drug product is packaged into laminated tubes with a [redacted] head and [redacted] child-resistant "push and turn" closure system (trade only; the sample tubes have a non-child-resistant container closure system). The applicant proposes to market 30g,

45g, and 60g tube sizes, along with 2g and 5g samples. Stability data support an expiry of 36 months for all but the 2g sample size, which will have an expiry of 18 months.

The Office of Compliance completed facilities inspections and issued an overall "Acceptable" recommendation.

The CMC reviewer, Dr. Raymond Frankewich, 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.

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 36 months for the 60, 45, 30 and 5 gm tubes, and 18 months for the 2 gm tube. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

No significant toxicity was noted in 13 week (mice, minipigs) or 9 month (minipig) dermal repeat dose studies. In the repeat dose oral toxicity studies, decreased weight and slight white matter vacuolation were seen in rats (27 week dosing), and decrease weight, mydriasis, and hypersalivation were seen in beagles (39 week dosing). Ivermectin was negative for mutagenicity in the Ames test, the mouse lymphoma assay, and an in vivo micronucleus test in rats. The 2-year dermal carcinogenicity study in mice was negative for neoplastic findings. The 2-year oral carcinogenicity study in rats found increased incidence of hepatocellular adenoma in males at 9mg/kg/d, but no findings at 1 or 3mg/kg/d. As the multiple of human exposure at 3mg/kg/d is ~600, the risk of carcinogenicity from clinical use of 1% ivermectin cream is expected to be minimal. Ivermectin was found to be teratogenic in rats and rabbits at maternal toxic doses and at multiples of human exposure of ~1900 and ~350, respectively. Labeling reflects Pregnancy Category C. In rats, ivermectin was excreted in the milk of nursing mothers and caused neonatal toxicity in the litters; however this may reflect the species-specific immaturity of the blood-brain barrier in rats at birth. Ivermectin cream, 1%, was found to be an irritant (under occlusion) to rabbit skin but a non-irritant to rabbit eyes, and a sensitizer but not a phototoxicant in guinea pigs.

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.

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

Soolantra (ivermectin) cream, 1.0%, is a topical product for the treatment of the inflammatory lesions of rosacea that is intended to be applied topically to the affected areas of the face once a day.

The formulation used in the clinical trials is identical to the marketed formulation; differences in manufacturing process were bridged via IVRT testing and do not impact product sameness (see above).

In Study RD.03.SRI.40064, the applicant investigated the systemic exposure to ivermectin from repeated (4 weeks) once daily topical facial application of 1 gram of ivermectin 1% cream in 15 evaluable subjects with severe papulopustular rosacea. Blood samples for pharmacokinetic analysis were obtained at hours 1,3, 6, 9, 12 and 24 hours post dose on days 0, 14 and 28, as well as in the post-treatment period. The mean ($\pm$standard deviation) value for C_{max} was 2.10 ($\pm$1.04) ng/mL, for T_{max} was 10 ($\pm$8) hours, and for AUC_{0-24} was 36.14 ($\pm$15.56) ng-h/mL. $T_{1/2}$ was 145 hours. The C_{max} and AUC_{0-24} values are substantially lower than those seen following oral administration of a single dose of ivermectin, albeit by cross-study comparison with Study RD.06.SRE.18120.

The applicant conducted a thorough QT/QTc study, RD.06.SRE.18120, to assess the effect of ivermectin (6mg oral dose). No effect on repolarization was identified.

Ivermectin is a substrate of CYP3A4. However, the impact of concomitant administration of drugs that are inhibitors of CYP3A4 is not expected to have clinical impact, as the systemic exposure from Soolantra cream has a greater than 60-fold margin of safety based on animal toxicity data.

The Clinical Pharmacology/Biopharmaceutics reviewer, Dr. Chinmay Shukla, found that the applicant met the requirements for approval from a clinical pharmacology perspective, and recommended *Approval* from a clinical pharmacology/biopharmaceutics perspective.

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

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials, Study 18170 and Study 18171, to establish the effectiveness of their product in the treatment of the inflammatory lesions of rosacea. These two studies, identical in design, were randomized, double-blind, parallel group studies with two parts: Part A, weeks 0-12, which was placebo-controlled, and Part B, weeks 13-52, which was active-controlled. The sponsor identified Part A as the pivotal part, and Part B as an extension to evaluate safety.

In Part A, 1371 adult subjects with rosacea, grade 3 (moderate) or 4 (severe) on the Investigator Global Assessment (IGA) Scale, and with 17 to 50 papules or pustules, applied study drug (Soolantra cream or vehicle cream) once daily for twelve weeks. The primary time

point was at twelve weeks. The primary efficacy measures were Investigator Global Assessment score and inflammatory lesion count. The co-primary endpoints were i) success rate, defined as the percentage of subjects who scored "Clear" or "Almost Clear" (score of 0 or 1) on the IGA scale at week 12, and ii) absolute change in lesion count from baseline to week 12.

The applicant was granted a Special Protocol Assessment, and a letter with agreements was issued on 22 October 2008. Agreements included:

- enrollment population of subjects with moderate to severe rosacea
- co-primary efficacy endpoints
  - proportion of subjects who achieve clear or almost clear and a 2-grade improvement on the 5-point IGA scale at week 12
  - absolute change in inflammatory lesion count from baseline to week 12
- secondary efficacy endpoints:
  - percent change in inflammatory lesion counts from baseline to week 12
  - nested analysis of co-primary efficacy endpoints at successively earlier time points
- sample size calculation
- ITT population as primary analysis population
- testing approach, sensitivity analyses, and multiplicity adjustment

The results for the co-primary efficacy endpoints are presented in the following table:

Endpoint	Study 18170			Study 18171		
	SOOLANTRA (N=451)	Vehicle (N=232)	P-value	SOOLANTRA (N=459)	Vehicle (N=229)	P-value
IGA Success n (%)	173 (38.4%)	27 (11.6%)	<0.001	184 (40.1%)	43(18.8%)	<0.001
Absolute change in inflammatory lesion counts Mean (SD)	20.5 (16.0)	12.0 (13.5)	<0.001	22.2 (14.9)	13.4 (14.5)	<0.001

Source: Adapted from Statistical Review and Evaluation, NDA 206255, Matthew Guerra, PhD, archived 8/29/14, p.10.

In Study 18170 and Study 18171, SOOLANTRA was superior to vehicle for the co-primary endpoints of i) success on the IGA and ii) absolute change in inflammatory lesions.

The reader is referred to the biostatistical and clinical reviews by Matthew Guerra, PhD, and Jane Liedtka, 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 Liedtka that the clinical trial data support a determination of efficacy.

8. Safety

Three thousand five hundred and forty six subjects with rosacea were exposed to ivermectin cream during the development program, including 910 subjects in the pivotal trials. Of the subjects with rosacea exposed to ivermectin cream, 1290 were exposed for at least 3 months, 771 for at least 6 months, and 250 for at least one year.

There were no deaths reported in the development program. One hundred and eleven serious adverse events (SAEs) were reported during the development program, 65 of which occurred in subjects receiving ivermectin cream; none were considered by the investigators to be related to the study drug. The medical reviewer, Dr. Jane Liedtka, reviewed the case narratives for each of the SAEs and concurred with the investigator assessments that the events were unlikely to be related to study drug.

In the pooled safety population comprised of 7 comparative studies up to 16 weeks, adverse events were reported at similar rates in the active and vehicle groups, 38% and 40% respectively. No adverse reactions (adverse events attributable to study drug and occurring more commonly in the active than the vehicle group) occurred at a frequency of greater than 1%. Adverse reactions reported in less than 1% of subjects include skin burning sensation and skin irritation; these will be included in labeling.

Neutropenia was investigated as a potential safety signal following the identification of neutropenia in three subjects during the open label safety study 40051 (which was discontinued as a precaution); in these three subjects, the neutropenia was not associated with clinical manifestations and resolved upon subsequent sampling. In three subsequent controlled studies, Study 40106 (vehicle controlled) and Studies 18170 and 18171 (vehicle controlled through week 12, active controlled through week 52), neutrophil counts were monitored but no drug-related neutropenia was identified.

A special safety concern is the risk of ingestion-type medication errors. The product will be marketed in trade size tubes of 30, 45 and 60 gms containing 300, 450 and 600 mg of ivermectin, respectively; physician samples of 2 and 5gms (20 and 50 mg of ivermectin, respectively) will also be produced. To reduce the risk of ingestion-type medication errors, the trade size tubes will have a child-resistant push-and-turn container closure system, and product labeling will include statements that the product is “not for oral… use” and “keep out of reach of children.”

The reader is referred to the clinical review by Dr. Jane Liedtka for a full review of the safety database, as well as to the biostatistical review by Dr. Matthew Guerra..

9. Advisory Committee Meeting

Not applicable, as no Advisory Committee meeting was held for this application because it did not raise controversial issues that would benefit from outside discussion.

10. Pediatrics

The applicant requested a full waiver from the requirement to perform pediatric studies based on the rationale that necessary studies would be highly impractical because of the small number of pediatric patients with rosacea. On July 2, 2014, the Division presented the applicant's position to the Pediatric Review Committee, who concurred with the applicant's request.

11. Other Relevant Regulatory Issues

Office of Scientific Investigation (OSI) audits were conducted at three sites. Audits at two of the sites were unremarkable. At the third site (Holly Harris, MD, site 1896), selected because of a discordance in the size of the treatment effect between the two co-primary endpoints (success on IGA disproportionately greater than absolute change in inflammatory lesions), the inspector identified that the investigator conducted the lesion counts prior to conducting assessment with the IGA scale, a reversal of the order specified in the protocol. Such an error would be expected to bias the investigator in favor of success when performing assessment with the IGA scale. Because the rationale for the selection of the site was consistent with the protocol violation identified, I requested the data from the sensitivity analysis that excluded the site in question, which are presented in the following table:

Endpoint	SOOLANTRA	Vehicle	P-value
IGA Success: n(%)			
Center 1896 only	11/20 (55%)	0/8 (0%)	
Overall			
With center 1896	173/451 (38.4%)	27/282 (11.6%)	<0.001
Without center 1896	162/431 (37.6%)	27/224 (12.1%)	<0.001
Absolute Change in Inflammatory Lesion Counts: Mean (SD)			
Center 1896 only	22.7 (9.6)	13.9 (6.9)	
Overall			
With center 1896	20.5 (16.0)	12.0 (13.5)	<0.001
Without center 1896	20.4 (16.2)	12.0 (13.7)	<0.001

Source: Dr. Matthew Guerra, email communication dated 10/21/2014

Removal of site 1896 resulted in a slightly lower proportion of subjects achieving success on the IGA, and had almost no impact on the results for absolute change in inflammatory lesion counts. Results remained highly significant for both co-primary endpoints, even after exclusion of site 1896.

There are no unresolved relevant regulatory issues.

12. Labeling

Dr. Carlos Mena-Grillasca of the Division of Medication Error Prevention and Analysis reviewed the proposed proprietary name under IND 76064 on 12 September 2013 and again under the NDA on 19 March 2014; he found the proposed proprietary name, Soolantra, to be acceptable.

All components of labeling were reviewed. Professional labeling conforms to the standards of the Physicians Labeling Rule. Patient labeling (Instructions for Use) was proposed and is appropriate for this product in order to inform patients about operation of the child-resistant container closure.

13. Recommendations/Risk Benefit Assessment

Regulatory action: *Approval*

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 206255 Soolantra (ivermectin) cream, 1.0% for the treatment of the inflammatory lesions of rosacea.

Risk-benefit assessment: The applicant established the efficacy and safety of Soolantra cream in the treatment of rosacea in two adequate and well-controlled trials, and provided sufficient information in their application to support product labeling. The robust efficacy of the product justifies the modest risks, the most serious of which appears to be the risk of ingestion-type medication errors.

Postmarketing Risk Evaluation and Management Strategies: 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 required.

Postmarketing requirements (PMR) and commitments (PMC): none

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/s/

JILL A LINDSTROM
12/19/2014