

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-502

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 17 th , 2010
From	Susan J. Walker, M.D., F.A.A.D Director, Division of Dermatology and Dental Products
Subject	Division Director Summary Review
NDA Supplement #	NDA 22-502 SN000
Applicant Name	Galderma Research and Development, Inc.
Date of Submission	March 2 nd , 2009
PDUFA Goal Date	January 1 st , 2010; (extension to April 2 nd , 2010)
Proprietary Name / Established (USAN) Name	Differin (adapalene)
Dosage Forms / Strength	Lotion, 0.1%
Proposed Indication(s)	Acne Vulgaris in patients 12 years of age and older
Action	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Amy Woitach (David Kettl – TL)
CDTL Review	David Kettl
Statistical Review	Mat Soukup (Mohamed Alesh – TL)
Pharmacology Toxicology Review	Kumar Mainigi (Barbara Hill – TL)
CMC Review/OBP Review	Rajiv Agarwal (Shulin Ding – TL)
Microbiology Review	N/A
Clinical Pharmacology Review	Julia Cho (Edward Bashaw – Director)
DDMAC	Andrew Haffer
OSE/DMEPA	Lori Cantin (Kristina Arnwine –TL)
Other	SEALD: Jeanne Delasko (Laurie Burke) DPV I: Tracy Salaam (Ida-Lina Diak – TL)

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This application is a 505(b) (1) submission proposing a new dosage form (lotion) for topical adapalene 0.1%. Topical adapalene 0.1% is currently approved in a solution, gel, and cream and topical adapalene 0.3% is currently approved as a gel for the treatment of acne vulgaris. This review presents/summarizes my concurrence with the discipline reviews. The application will be approved.

2. Background

Adapalene binds to specific retinoic acid nuclear receptors but does not bind to cytosolic receptor proteins. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes. However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne vulgaris is unknown. Although the exact mechanism of action is unknown, topical adapalene is thought to normalize the differentiation of follicular epithelial cells and to affect terminal differentiation of keratinocytes.

The phase 3 clinical program consisted of two studies (Studies 18113 and 18114), to assess the safety and efficacy of adapalene 0.1% lotion compared to its vehicle with the objective of establishing the superiority of adapalene 0.1% lotion to vehicle in the treatment of acne vulgaris. In both studies, adapalene 0.1% lotion was statistically superior to vehicle for achieving “success” on the Investigators Global Assessment and lesion counts.

3. CMC

On December 18th, 2009 an overall recommendation of “WITHHOLD” was documented on the Establishment Evaluation Request. A control testing laboratory was not ready for inspection, as there was no method transfer and no analytical work done. This has been resolved and an overall recommendation of “acceptable” has been issued from Office of Compliance. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology 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. The information submitted for the PK trial conducted for this lotion formulation of adapalene, as well as the referenced studies conducted for previously approved formulations, only included subjects as young as 18 years of age. No pharmacokinetic data is available for any adapalene product for adolescents. Though most of the samples in adult PK studies for adapalene products were below the limit of quantitation, and the concern that this population will be different is low, it would be optimal for the PK information provided by the applicant to mirror the population for which this product is approved. The applicant has agreed to a post-marketing commitment to conduct a study to obtain pharmacokinetic data for adolescents aged 12 years to 17 years who have acne vulgaris treated with Adapalene 0.1% lotion (adapalene) lotion, 0.1% under maximal use conditions.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The sponsor has submitted information from two adequate and well controlled clinical trials establishing that use of adapalene 0.1% lotion is safe and effective for treatment of acne vulgaris in subjects 12 years and older.

A total of 1608 subjects were enrolled in studies 18113 and 18114, comparing adapalene 0.1% lotion with vehicle. Endpoints evaluated included acne lesions counts and the investigator's global assessment. In both studies, adapalene 0.1% lotion established superiority to vehicle for the treatment of acne vulgaris.

The efficacy primary endpoint outcomes are summarized in the following tables from the Agency Biostatistics review by Dr. Soukup:

Table 5: Investigator Global Results (ITT-LOCF)

	Study 18113		Study 18114	
	Differin™ Lotion (N = 533)	Vehicle Lotion (N = 542)	Differin™ Lotion (N = 535)	Vehicle Lotion (N = 531)
IGA Success (%)	140 (26.3)	94 (17.3)	129 (24.1)	87 (16.4)
p-value [†]	-	< 0.001	-	0.001

[†] P-value is based on CMH stratified on “analysis center”.

Source: Study Report Table 11.4.1.1-1; reproduced by reviewer using ADGA.XPT

Table 6: Change in Total Lesion Counts (ITT-LOCF)

	Study 18113		Study 18114	
	Differin™ Lotion (N = 533)	Vehicle Lotion (N = 542)	Differin™ Lotion (N = 535)	Vehicle Lotion (N = 531)
Mean Change	37.9	26.7	32.4	23.4
Mean Percent Change	51.5	37.1	44.6	32.8
p-value [†]	-	< 0.001	-	< 0.001
p-value [‡]	-	< 0.001	-	< 0.001

[†] P-value is based on the ANCOVA model on rank data of changes from baseline lesion counts, including rank data of baseline lesion count as a covariate, treatment and “analysis center” as main effects.

[‡] P-value is based on using an ANCOVA model with main effects only on the unranked data.

Source: Study Report Table 11.4.1.1-1; reproduced by the reviewer using ADLS.XPT.

Table 7: Change in Inflammatory Lesion Counts (ITT-LOCF)

	Study 18113		Study 18114	
	Differin™ Lotion (N = 533)	Vehicle Lotion (N = 542)	Differin™ Lotion (N = 535)	Vehicle Lotion (N = 531)
Mean Change	14.7	10.6	12.7	10.2
Mean Percent Change	54.9	40.3	46.0	36.9
p-value [†]	-	< 0.001	-	< 0.001
p-value [‡]	-	< 0.001	-	< 0.001

[†] P-value is based on the ANCOVA model on rank data of changes from baseline lesion counts, including rank data of baseline lesion count as a covariate, treatment and “analysis center” as main effects.

[‡] P-value is based on using an ANCOVA model with main effects only on the unranked data.

Source: Study Report Table 11.4.1.1-1; reproduced by the reviewer using ADLS.XPT.

Table 8: Change in Non-Inflammatory Lesion Counts (ITT-LOCF)

	Study 18113		Study 18114	
	Differin™ Lotion (N = 533)	Vehicle Lotion (N = 542)	Differin™ Lotion (N = 535)	Vehicle Lotion (N = 531)
Mean Change	23.2	16.1	19.6	13.1
Mean Percent Change	49.6	35.7	43.1	30.2
p-value [†]	-	< 0.001	-	< 0.001
p-value [‡]	-	< 0.001	-	< 0.001

[†] P-value is based on the ANCOVA model on rank data of changes from baseline lesion counts, including rank data of baseline lesion count as a covariate, treatment and “analysis center” as main effects.

[‡] P-value is based on using an ANCOVA model with main effects only on the unranked data.

Source: Study Report Table 11.4.1.1-1; reproduced by the reviewer using ADLS.XPT.

8. Safety

There were no significant or novel safety issues for adapalene in this dosage form. A total of 1382 subjects were exposed to adapalene 0.1% lotion during the development program. No deaths occurred in the clinical development program. Significant adverse events considered related to the study drug were not reported for organ systems other than skin and subcutaneous tissue.

Topical safety was adequately evaluated and included assessment for local tolerability and dermal safety studies to evaluate contact sensitization and irritation. Assessment of phototoxicity and photoallergenicity relied upon previous studies demonstrating adapalene outcomes. This application establishes the safety of adapalene 0.1% lotion for treatment as labeled with this approval.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application.

10. Pediatrics

The Pediatric Review Committee concurs with the recommendation for a partial waiver for patients 0-11 years of age.

11. Other Relevant Regulatory Issues

There are no other unresolved regulatory issues

12. Labeling

There are no unresolved labeling issues. Final printed labeling will be attached to the approval letter.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval
- Risk Benefit Assessment – The benefits of treatment with this product outweigh the risks.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None
- Recommendation for other Postmarketing Requirements and Commitments – Applicant has agreed to conduct a postmarketing study to obtain pharmacokinetic data for adolescents aged 12 years to 17 years who have acne vulgaris treated with adapalene lotion, 0.1% under maximal use conditions

Susan J. Walker, M.D., F.A.A.D
Director
Division of Dermatology and Dental Products

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22502

ORIG-1

GALDERMA
RESEARCH AND
DEVELOPMENT
INC

DIFFERIN LOTION

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
03/17/2010