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RESEARCH**

APPLICATION NUMBER:
22-502

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 4, 2009
From	David Kettl, MD; Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-502 (Related IND: 76,057)
Supplement#	SN 000
Applicant	Galderma Laboratories, LP
Date of Submission	March 2, 2009
PDUFA Goal Date	January 1, 2010
Proprietary Name / Established (USAN) names	Differin (adapalene) Lotion 0.1%
Dosage forms / Strength	Topical lotion
Proposed Indication(s)	Acne vulgaris in patients 12 years of age and older
Recommended:	<i>Approval</i>

1. Introduction

This application is a 505(b)(1) application for Differin (adapalene) Lotion 0.1% for the treatment of acne vulgaris in patients 12 years of age and older. The application is for a new dosage form, lotion, for adapalene.

Adapalene is approved for the topical treatment of acne vulgaris in patients 12 years of age and older and has been marketed by Galderma Laboratories in the following dosage forms:

0.1% solution	(NDA 20-338)	approved 5/31/1996, now discontinued
0.1% gel	(NDA 20-380)	approved 5/31/1996
0.1% cream	(NDA 20-748)	approved 5/26/2000
0.3% gel	(NDA 21-753)	approved 6/19/2007

...and in a combination product,

Epiduo Gel (Adapalene 0.1%/Benzoyl Peroxide 2.5 %) (NDA 22-320), approved 12/8/2008.

Adapalene is a naphthoic acid derivative with retinoid-like and anti-inflammatory properties. Topical adapalene is thought to normalize the differentiation of follicular epithelial cells, resulting in decreased microcomedone formation. Related products for the treatment of acne include tretinoin and tazarotene.

The phase 3 clinical program consisted of two studies (Studies 18113 and 18114), to assess the safety and efficacy of Differin Lotion compared to its vehicle with the objective of establishing the superiority of Differin Lotion to vehicle. In both studies, Differin was statistically superior to its vehicle for the percent of IGA successes and the change in all lesion counts primary analysis as well as several supportive and sensitivity analyses.

As the clinical team leader and CDTL for this application, I concur with the recommendation of Dr. Amy Voitach, the primary clinical reviewer, that this application should be approved, pending the final recommendation by the Office of Compliance regarding facility inspections.

2. Background

The development plan for this application was discussed with the applicant at a Pre-IND meeting March 2, 2007, and at an End of Phase 2 meeting on August 7, 2007. A Pre-NDA meeting was scheduled for February, 2009, but was cancelled by the sponsor.

There was general agreement on clinical endpoints for the phase 3 trials as a result of these meetings, and while no agreements were reached on the necessity for long range trials or for photo-related dermal safety trials, the sponsor rationale was deemed reasonable. The current application includes further information that supports the waiver for these requirements. No requests for special protocol assessments were submitted by the applicant.

Product development for this application was initiated with the submission of the initial pharmacokinetic study to IND 76,057 in April, 2007.

Five trials above were conducted in support of this application. Two phase 3 trials were conducted for demonstration of efficacy and safety. Additionally, the following studies were conducted with regard to safety:

- Two dermal safety studies in healthy subjects (18110, 18111).
- One pharmacokinetic study in subjects with acne vulgaris (18108).

The trials conducted for this application are summarized in the following table:

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Trial ID	Design	Dosing/ Duration	Severity	Number of Sites	Number of Subjects Enrolled	Subject Age	Primary Endpoint/ Objective
113	Randomized, double-blind, vehicle controlled	Once daily for 12 weeks	Subjects had, excluding the nose, ≥ 20 , ≤ 50 , papules and pustules on the face and ≥ 30 , ≤ 100 , non-inflammatory on the face. Subjects also had an IGA of 3 (moderate) or 4 (severe).	39	1075 533 adapalene 542 vehicle	12-50 years old	Two co-primary efficacy endpoints: Two-point reduction from baseline to week 12 in IGA score and the absolute change from baseline to week 12 in inflammatory, non-inflammatory, and total lesion counts (demonstrating a reduction of 2 of the 3 lesion counts).
114	Randomized, double-blind, vehicle controlled	Once daily for 12 weeks	Subjects had, excluding the nose, ≥ 20 , ≤ 50 , papules and pustules on the face and ≥ 30 , ≤ 100 , non-inflammatory on the face. Subjects also had an IGA of 3 (moderate) or 4 (severe).	36	1066 535 adapalene 533 vehicle	12-64 years old	Two co-primary efficacy endpoints: Two-point reduction from baseline to week 12 in IGA score and the absolute change from baseline to week 12 in inflammatory, non-inflammatory, and total lesion counts (demonstrating a reduction of 2 of the 3 lesion counts).
108	PK study	2 g once daily/30 days	Subjects had minimum of 20 inflammatory lesions on the face (excluding the nose) and 30 non-inflammatory lesions on the face (excluding the nose). Subjects also had an IGA of 4 (severe).	1	14	18-35 years old	Assess the systemic exposure to Adapalene during topical application of Adapalene Lotion, 0.1%
110	Dermal irritation	0.2 g for 5 days/wk for 15 applications over 21 days	Healthy subjects	1	50 44 completed	18-65 years old	Dermal safety
111	Dermal sensitization	Induction: 3 days/wk for 3 weeks (total of 9 applications) Challenge: after 7-18d, occlusive patches applied for 48 hrs.	Healthy subjects	1	203	18-65 years old	Dermal safety

3. CMC/Device

The CMC review of this NDA concluded that the applicant provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. However, there were two pending issues when the CMC review was closed:

- The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is pending. *(This final report is anticipated November 30, 2009, after the closure of the clinical and CDTL reviews, but well in advance of the PDUFA date for this application.)*
- Required information on the carton and container closure labels is not in the recommended format and must be presented as recommended. *(This information was received October 28, 2009, and was deemed acceptable.)*

The drug substance is adapalene, which is available as a white to off white powder, manufactured in (b) (4). The drug substance manufacturing site has been classified as acceptable based on profile. As noted above, the final recommendation from the Office of Compliance remains pending as of the date of this review.

The drug product, Differin Lotion, 0.1%, is a white to off-white lotion for the topical treatment of acne vulgaris. It contains adapalene at the strength of 0.1% by weight (w/w).

A complete description of the quantitative composition of the finished product is provided below.

Ingredient	Grade	Function	Theoretical Weight (mg/g)	Theoretical Percentage (w/w)	
Adapalene	_ 1	Active Ingredient	1.0	0.1	
Disodium Edetate	USP	(b) (4)			
Propylparaben	NF				
Carbomer 9 ^(b) 1	NF				
Methylparaben	NF				
Poloxamer 124	NF				
Phenoxyethanol	NF				
Stearyl Alcohol	NF				
PPG-12/SMDI Copolymer ²	_ 1				
Propylene Glycol	USP				
Polyoxyl-6 & Polyoxyl-32 Palmitostearate	_ 1				
Medium Chain Triglycerides	NF				
Sodium Hydroxide	NF				
Purified Water	USP				
Total				1000.0	100.0

¹ Testing will be performed per Galderma Production Canada, Inc. (GPCI) in-house monograph.

(b) (4)

Differin Lotion, 0.1% is provided in 0.5-oz (~15g), 2-oz (~60g) and 4-oz (~120g) bottles equipped with a dispensing cap. The 0.5-oz bottles will be used as physician samples and the 2-oz and 4-oz bottles provided with a pump will be the commercial packaging.

All but two excipients in Differin Lotion, 0.1% are compendial grades. These two excipients, (b) (4) were judged to be within acceptable ranges by the CMC review team. The two non-compendial excipients are also well characterized and supported by the Pharmacology/Toxicology review as noted by Dr. Mainigi.

The CMC review by Dr. Agarwal concurred that the dosage form is indeed a lotion and had satisfactory rheological profiles, and “is pourable, flows, and conforms to its container at room

temperature.” While the product is technically a drug suspended in a lotion and not dissolved, the CMC review team received satisfactory information that the drug product could be accurately labeled as a lotion without qualifiers in the carton and container labeling.

Documents supporting the container closure system and its labeling have been reviewed since the closure of the CMC review and were deemed acceptable.

Galderma claims an exclusivity period of 3 years commencing on the date of approval of this supplemental application.

The only approvability issue from a CMC perspective is:

The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is pending. (*This final report is anticipated November 30, 2009, well in advance of the PDUFA date for this application.*)

4. Nonclinical Pharmacology/Toxicology

The conclusion of the Pharmacology/Toxicology review by Dr. Mainigi is that Differin Lotion 0.1% was well tolerated from a nonclinical safety perspective and there are no outstanding nonclinical safety issues relevant to clinical use.

A wide spectrum of topical and systemic studies (numbering over 100) was conducted to support the safety of several approved formulations (0.1% solution, cream and gel, 0.3% gel and Epiduo a combination gel of 0.1% adapalene and 2.5% benzoyl peroxide) of adapalene. The human use of these products was further supported by multiple clinical studies involving thousands of normal healthy subjects and patients with *acne vulgaris*. Some of these globally used formulations are in the market for over a decade; however, to date no severe adverse effects have been reported.

Adapalene is a synthetic naphthoic acid derivative and exhibits biological activities similar to retinoids despite some differences between adapalene and retinoids like tretinoin. Adapalene binds to specific retinoic acid nuclear receptors, but unlike tretinoin it does not bind to cellular retinoid binding protein II. Second, in gene transactivation assays, tretinoin exhibited equally strong transcriptional activation of all three retinoic acid receptors, while the activity of adapalene for RAR α was much lower. 9-*cis*-retinoic acid is a physiologic ligand of tretinoin, not adapalene. In addition to displaying typical retinoid like effects (e.g. normalization of the maturation of follicular epithelium), adapalene also exhibits anti-inflammatory properties.

In most species, no significant drug accumulation was observed in the dermal studies of any duration. The low drug accumulation on repeated applications indicated fast metabolism.

In the 3-month minipig dermal study conducted with Differin Lotion 0.1% (0.0, 0.2, 0.6, and 1.2 mg adapalene/kg/day), absolutely no systemic toxicity was observed at the highest dose level. The NOAEL for systemic and local toxicity was established at 1.2mg/kg.

Assuming 100% absorption, the maximum recommended therapeutic dose of 2 grams of 0.1% adapalene lotion will provide 0.033 mg systemic drug/kg/day, an amount 36 times lower than the NOAEL in minipigs; in terms of body surface area, the margin of safety will be 26 times. In humans, the dermal absorption has never exceeded 5% of the applied dose; therefore, the actual margin of safety will be much greater.

In two local tolerance studies Differin Lotion 0.1% caused moderate irritation in rabbits and delayed contact hypersensitivity in guinea pigs.

Adapalene did not exhibit mutagenic or genotoxic effects *in vivo* (mouse micronucleus test) and *in vitro* (Ames test, Chinese hamster ovary cell assay, and mouse lymphoma TK assay) studies.

In the mouse dermal carcinogenicity study, no drug-related neoplastic lesions were observed. In the rat oral carcinogenicity study, the high-dose males (1.5mg/kg/day) exhibited a significant ($p < 0.05$) incidence of benign pheochromocytoma of the adrenals. The combined number of benign and malignant pheochromocytoma, and pancreatic islet cell tumors in drug-treated males indicated a higher incidence. The high incidence of pheochromocytoma is a characteristic of compounds acting like retinoids. A high incidence of carcinomas and adenomas of thyroid was also observed in the drug treated females.

No photocarcinogenicity study was conducted.

In the oral studies (1.5-20mg adapalene/kg/day), no effects on reproductive performance, fertility, litter size, growth, development, weaning, and subsequent reproductive performance of the offspring were observed.

In the dermal teratology studies (6mg adapalene/kg/day) in rats and rabbits, no teratologic changes were observed. However, in the oral rat and rabbit studies (5, 25, and 60mg adapalene/kg/day), significant teratologic changes (skeletal and visceral malformations) were recorded at 25mg/kg/day and higher dose levels. In rats, the placenta acted as a partial barrier to drug and its metabolites during organogenesis and thereafter. Adapalene is also secreted in the milk of rats. In the prenatal and postnatal development studies (0.15, 1.5, and 15mg adapalene/kg/day), the highest dose of adapalene had no effect on the evaluated litter parameters (development after weaning, mating and fertility) of F₀ and F₁ generations, and on F₂ fetuses. Since adapalene was excreted in the milk, it is inferred that the pups were exposed both *in utero* and during lactation.

Nonclinical sections of the product labeling are virtually identical to the related adapalene topical products.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review by Dr. Cho concluded that the information provided by the sponsor was adequate and that the applicant's request to waive QT/QTc studies is acceptable from the clinical pharmacology standpoint, supported by a demonstration of low systemic exposures to adapalene.

Systemic exposures of adapalene 0.1 % gel and 0.1 % cream have previously been studied in acne patients treated once daily to ~1000 cm² BSA for 5 – 30 days with 2 g per day. Review of the package inserts of these products showed that the absorption of adapalene was low and most samples contained adapalene below the limit of quantitation.

There was no dose-ranging study conducted for Adapalene Lotion in product development.

The applicant submitted one PK study and one *in vitro* dermal penetration study along with the results of two dermal safety tests and two phase 3 safety and efficacy studies. The sponsor also referenced 3 study reports submitted for earlier NDAs (Gel 0.3 % and Epiduo (Adapalene, 0.1%/Benzyl Peroxide, 0.25 %), which include two *in vivo* PK and one skin stripping studies.

The Phase 1 clinical pharmacology study in this submission (SPR. 18108) is an open labeled PK study to assess the systemic exposure to adapalene lotion, 0.1% in 14 subjects (7 male and 7 female) between 18 and 35 years old with severe acne vulgaris. Adapalene was applied once daily for 30 days on the face, back and chest (simulating a maximum use condition), 2 g/day, covering a 1000 cm² application area (approximately 2 mg/cm²).

All plasma concentrations from 12 of the 14 subjects studied were less than 0.1 ng/mL (the limit of quantification), and all plasma concentrations from the other two subjects were less than 0.131 ng/mL.

While the *in vitro* dermal penetration assays have inherent limitations and are not considered as a validated method to evaluate dermal absorption by the Agency, the results were supportive and showed the penetration of adapalene lotion, 0.1% formulations was lower than the total penetration of Differin Gel, 0.1%, but a higher total penetration compared to Differin Cream, 0.1%.

The applicant also submitted a cross study analysis of the plasma exposure of adapalene lotion 0.1 % with the previously reported adapalene gel 0.3 %. This analysis also has inherent limitations in conclusions, but it was shown that the frequency and concentrations of adapalene detected in plasma following adapalene lotion 0.1 % were notably lower than those of adapalene gel 0.3 %, and it is consistent with what is expected from the dose-response.

This PK comparison was concluded to provide supportive evidence for the safety of the currently proposed formulation.

The clinical review team concurred with the presented applicant rationale, as well as the lack of post-marketing adverse event reporting for arrhythmias and EKG changes for related adapalene formulations, that no additional QT/QTc information was necessary to approve this application. The most recently approved product containing adapalene, Epiduo, did not conduct any QT related studies.

Notable Issue Related to Clinical Pharmacology/Biopharmaceutics:

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 should be necessary for the PK information provided by the applicant to mirror the population for which this product could be approved. It is recommended that a post-marketing study be conducted to obtain PK data for adolescents who have acne vulgaris.

6. Clinical Microbiology

Not applicable for this application.

7. Clinical/Statistical- Efficacy

Two phase 3 trials were conducted to demonstrate efficacy for Differin Lotion 0.1%. Studies 18113 and 18114 were used to assess the safety and efficacy of Differin Lotion compared to its vehicle with the objective of establishing the superiority of Differin Lotion to vehicle. The endpoints were discussed with the division and agreed upon during the review of the protocol. The primary efficacy endpoints were:

Change from Baseline in two out of three lesion counts (total, inflammatory and non-inflammatory) after accounting for multiplicity adjustment.

And

Percent of subjects with an IGA success defined as a Week 12 two grade improvement from baseline.

1068 subjects were exposed to Differin Lotion in the two phase 3 trials. Overall, the mean age of subjects was 19 years old; approximately 65% of subjects were identified as Caucasian; and 54% of subjects were female. The most prevalent skin phototype was Type III which

accounted for approximately 34% of subjects. There was no imbalance of any of the demographic factors between treatment arms.

In both studies, Differin was statistically superior to its vehicle for the percent of IGA successes and the change in all lesion counts for the protocol defined primary analysis as well as several supportive and sensitivity analyses.

The observed treatment effects for the dichotomized IGA were 9.0% ($p < 0:001$) and 8.0% ($p = 0:001$) for studies 18113 and 18114, respectively. The treatment effects for the mean absolute change in total lesions were 11.2 and 9.0 lesions; in inflammatory lesions were 4.1 and 2.5 lesions; in non-inflammatory lesions were 7.1 and 6.5 lesions in studies 18113 and 18114, respectively.

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 TM Lotion (N = 533)	Vehicle Lotion (N = 542)	Differin TM 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 TM Lotion (N = 533)	Vehicle Lotion (N = 542)	Differin TM 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.

The results of the subgroup analyses by age group (12 to 17 years of age and 18 to 64 years of age), gender (male and female), and race (Caucasian and non-Caucasian), support the conclusion that the overall efficacy profile of Differin Lotion is superior to vehicle lotion across all subgroups. In general, older subjects (18 – 64 years of age), female subjects, and Caucasian subjects were more likely to have IGA successes and greater lesion count reductions than were the opposing subjects within the same subset categorizations.

The clinical review team identified the clinical study site of [REDACTED] (b) (6) as having a financial conflict of interest. Based upon this finding, the team recommended a DSI inspection of this study site from study [REDACTED] (b) (6). However, DSI recommended that this center not be inspected as the site had been subject to a recent inspection with no issues identified. Agency statistical analysis excluding the [REDACTED] (b) (6) subjects from this study site did not change the statistical results or conclusions of study [REDACTED] (b) (6). The clinical team concurs that this conflict of interest does not impact the efficacy or safety conclusions of this study.

8. Safety

Five clinical studies (three Phase 1 and two Phase 3) were conducted to evaluate the safety of Differin Lotion, 0.1%. These studies exposed an adequate number, 1382 subjects, to Differin Lotion.

Topical safety was adequately evaluated in the development program and included an assessment for local tolerability and dermal safety studies to evaluate contact sensitization and irritation. Safety data for phototoxicity and photoallergenicity relied on previous studies conducted for other Differin products which demonstrate photosensitivity and are labeled as such. The proposed label for Differin Lotion contains the same precautions, and the clinical review team concurs that additional studies for phototoxicity and photoallergenicity were not necessary for this application.

No deaths occurred in the clinical development program. Five serious adverse events (SAE's) were reported in study 18113 and no SAE's were reported in study 18114. Three of the serious adverse events (depression, multiple drug overdose, cerebral hemorrhage) occurred in 2 subjects being treated with Differin, did not result in discontinuation from the study and are not likely related to the study drug. Significant AE's considered related to the study medication were not reported for organ systems other than skin and subcutaneous tissue.

Ten subjects discontinued Differin Lotion therapy in the phase 3 trials compared with three subjects in the vehicle groups. In study 18113, six subjects within the Differin treatment group discontinued because of AE's including acne (two subjects), skin irritation (two subjects), irritant contact dermatitis on the face (one subject), and periocular skin burning sensation, skin discomfort, and skin swelling (all three events were reported by one subject). Within the lotion vehicle treatment group, one subject discontinued because of possible allergic contact dermatitis and one subject because of skin irritation.

In study 18114, four subjects within the Differin treatment group discontinued because of AEs including acne (two subjects), skin discomfort (one subject), and oral herpes (one subject). Within the lotion vehicle treatment group, one subject discontinued because of acne.

Non-dermatologic side effects were similar between the active adapalene lotion and its vehicle.

The local tolerability of Differin appears to be slightly more irritating than its vehicle with most irritation (dryness, erythema, scaling, and stinging) occurring within the first week of treatment. While the mean level of irritation for Differin does appear to be highest at Week 1, the mean is still scored below a mild rating. Irritation tends to resolve by the end of treatment (Week 12) reaching near baseline levels.

Adapalene is a widely marketed acne product in its various previous approved formulations and its adverse event profile is reasonably well understood. The common side effects of skin irritation, dryness, erythema, burning and scaling were mirrored in this application and are not unexpected. The reported adverse event experience and local tolerability for Differin Lotion, 0.1% are comparable to other approved Differin products.

This CDTL review concurs with the primary clinical and biostatistics reviewers that these safety issues can be adequately addressed by product labeling and that a satisfactory risk/benefit profile for adapalene lotion has been demonstrated by the applicant.

Adverse event table recommendations for labeling:

Combined Study 1 and Study 2	Maximum Severity During Treatment (N = 1057)			Week 12 Treatment Severity (N = 950)		
	Mild	Moderate	Severe	Mild	Moderate	Severe (b) (4)
Local Cutaneous Irritation (skin irritation)						
Erythema						
Scaling						
Dryness						
Stinging/burning						

9. Advisory Committee Meeting

No Advisory Committee meeting was held for this application.

10. Pediatrics

The applicant requested a waiver for subjects younger than 12 years of age. While the Division has recently concluded that acne vulgaris occurs with some frequency as early as the onset of puberty around nine years of age in some patients, the sponsor was not informed of

any requirements to study subjects from ages 9-12 during several meetings with the Agency. No other adapalene products have been studied down to 9 years of age, and all the previously approved adapalene products carry the same population information for ages 12 years and above. The clinical reviewer recommends, and I concur, that approval be granted for the population of patients 12 years and above and waived under 12 years.

The Pediatric Review Committee met on November 4, 2009. The PeRC agreed with the Division recommendation, granted the partial waiver for patients 0-11 years of age and concurred that the product is adequately labeled.

11. Other Relevant Regulatory Issues

There were no issues with financial disclosures or GCP guidelines.

No other regulatory issues remain outstanding as of the close of this CDTL review.

12. Labeling

Labeling negotiations are ongoing with the sponsor at the date of this review.

Consultation with DDMAC emphasized clarification of the “lotion” dosage form in the prescribing information. The CMC conclusion was that this was a lotion, but noted that the adapalene particles were suspended, as opposed to being dissolved, in a oil-in-water emulsion. Dr. Haffer also commented in his review that the Section 17 Patient Counseling information should approximate that of the Differin Gel 0.3% labeling.

The OSE consultations regarding carton/container labeling and the prescribing information are still pending at the closure of this CDTL review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The clinical team leader concurs with the primary clinical reviewer that this product should be approved for the indication of acne vulgaris in patients 12 years of age and older.

- Risk Benefit Assessment

The efficacy for the indication of acne vulgaris in patients 12 years of age and older has been adequately demonstrated. The safety findings in the trials approximate those of the previous experience with topical adapalene 0.1% products.

The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond agreement on product labeling and the need for an acceptable Office of Compliance inspection report involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations.

The applicant has not yet been notified regarding the need for a post-marketing study be conducted to obtain PK data for adolescents who have acne vulgaris with adapalene lotion.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not required for this product

- Recommendation for other Postmarketing Requirements and Commitments

It is recommended that a post-marketing study be conducted to obtain PK data for adolescents who have acne vulgaris treated with adapalene lotion down to a lower age limit of 12 years of age under maximal use conditions.

The protocol for such a study should be submitted by June 2010.

The protocol should be initiated by November 2010.

The study results should be submitted to the FDA by June 2011.

- Recommended Comments to Applicant

There are no other recommended comments exclusive of proposed labeling in PLR format. Labeling discussions are ongoing with the sponsor as of the date of this review.

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/

DAVID L KETTL
11/10/2009