The DDRE review of September 8, 2006 agrees with this principle conclusion, stating "Based on our previous analysis and the additional information provided in the sponsor's submission, DDRE does not find a compelling safety signal for retinoid-specific birth defects associated with topical adapalene use from the AERS reports alone"

- *The calculations of the safety margin under reasonable expected use conditions make this risk assessment extremely conservative. The selection of supernumerary ribs as the animal endpoints should not be viewed as definitive.*

The safety margins are, in fact, conservative and are subject to interpretation. The lack of sufficient data to discount the likelihood of increased systemic exposure leading to more malformations can still be addressed by the sponsor by completing a systemic exposure assay using the more sensitive methodology.

- *Pregnancy labeling that "over-warns" can lead to the unintended tragic consequences of the termination of a highly desired pregnancy.*

This statement is true, but may not apply to this product until sufficient data show that the labeling indeed "over-warns" (versus appropriately warning) the physicians and patients guided by the labeling.

Again, no other supporting evidence or documentation is provided in the current meeting request letter other than the review of 163 adapalene exposed pregnancies outlined above.

Pregnancy and Maternal Health Staff Consultation:

At the request of the Division, the PMHS was consulted regarding the pregnancy labeling for adapalene 0.3 % gel. Their conclusion is as follows:

> Based on the lack of additional animal data, low systemic exposure and no compelling evidence of teratogenicity of the 0.1% topical formulations, the *PMHS recommends no change in the pregnancy category if the adapalene 0.3% topical gel is approved.* Using different pregnancy categories for topical formulations of the same product may lead to prescriber and user confusion. Having the 0.1% gel and cream labeled as a category C and the 0.3% gel labeled as a category [ ] implies that we have reviewed more data than we have actually reviewed.
>
> The following labeling is recommended:
>
> ***Pregnancy: Teratogenic effects, Pregnancy Category C.*** [ ]

[ ]

Of note, the current adapalene 1% topical gel and cream labels do not include any information regarding the potential risk of adapalene based on the chemical class (retinoid). [

[ ]

Conclusions and Recommendations for Regulatory Action:

This reviewer agrees with the PMHS consultation that pregnancy category C is acceptable for both the adapalene 0.1% and 0.3% formulations if satisfactory labeling can be agreed to with the sponsor.

A class labeling statement such as "*Retinoids may cause fetal harm when administered to pregnant women*" may be appropriate for both formulations.

[ ]

Recommended comments to be conveyed to sponsor:

In your Complete Response to the February 1, 2005 non-approval action letter, please submit the following items:

1. [ ]

2. The draft labeling may have wording that provides for Pregnancy Category C if the revised labeling adequately addresses concerns that increased systemic exposure might increase the teratogenic risk to pregnant patients. Please submit proposed labeling which will incorporate the suggested pregnancy section:

Pregnancy: Teratogenic effects, Pregnancy Category C. [

[ ]

3. Please provide information that addresses the relative dermal safety for the two products.
4. A pharmacokinetic study comparing systemic absorption of the 0.1 % and 0.3% gels under maximal use conditions, using the newer, more sensitive analytical method *(LOQ ≤ 0.1 ng/mL)* should be performed as recommended at the April 13, 2005 teleconference.
5. Comparison of efficacy claims between the 0.1% gel and the 0.3% gel may be limited given the marginal increase in efficacy shown in the data reviewed at the October 12, 2005 guidance meeting. The sponsor is referred to the Biostatistics comments from that guidance meeting.
6. The sponsor should continue to monitor adapalene exposed pregnancies for evidence of retinoic acid embryopathy and provide such information in a Safety Update.

David Kettl, MD
Medical Officer

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

/s/

David Kettl
12/1/2006 02:14:14 PM
MEDICAL OFFICER

Markham Luke
12/4/2006 01:00:11 PM
MEDICAL OFFICER
Sponsor will need to submit a Complete Response supported by informaton requested in NA letter & subsequent meetings to allow for formal review of the NDA approvability issues.
See Team Leader signature comments to be conveyed to sponsor.

Susan Walker
12/11/2006 03:35:34 PM
DIRECTOR
Applicant will be sending "complete response". Agency comments will go out after review of complete response.

CLINICAL REVIEW

Application Type: NDA
Submission Number: 21-753
Submission Code: 000

Letter Date: December 18, 2006
Stamp Date: December 19, 2006
PDUFA Goal Date: May 19, 2007

Reviewer Name: David Kettl, MD
Through: Susan Walker, MD, DDDP Division Director
Review Completion Date: March 29, 2007

Established Name: Adapalene 0.3% Gel
(Proposed) Trade Name: Differin Gel 0.3%
Therapeutic Class: Topical synthetic retinoid
Applicant: Galderma Laboratories, LP

Priority Designation: S

Formulation: Topical Gel
Dosing Regimen: Daily application to [redacted] skin
Indication: Topical treatment of acne vulgaris
Intended Population: Patients 12 years of age and older

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Differin (adapalene) Gel, 0.3% be approved for the topical treatment of acne vulgaris in patients twelve years of age and older.

The applicant, Galderma Laboratories, LP, addressed the deficiencies specified in the Agency "not approvable" letter dated February 1, 2005. The Agency has accepted that adequate evidence from the applicant has been presented to demonstrate statistical superiority over the currently approved Differin (adapalene) Gel 0.1% utilizing the pre-specified GEE analysis. However, various Agency analyses demonstrated the lack of statistical significance in improvement in lesion counts. This reviewer concludes that the efficacy advantage is minimal compared to the existing Differin 0.1% product.

The applicant submitted pregnancy exposure data in the complete response to the February, 2005 non-approval action. While there is no compelling evidence of teratogenicity of the 0.1% topical product, and no pattern of retinoid embryopathy in the few pregnancies inadvertently exposed to Differin 0.3% gel, the data is not yet sufficient to conclude that there is no increased risk from the higher concentration. Continued monitoring of exposed pregnancies [ ] should be considered as a post-marketing commitment to document the possible teratogenic effects of both formulations of Differin gel.

This reviewer concurs with the Biopharmaceutics reviewer position that a study to fully assess the systemic exposure of the 0.3% concentration be conducted in order to "*not only provide information to guide the safety assessment of 0.3% adapalene gel relative to the approved 0.1% gel product, but also provide valuable dose/exposure-response relationship information for adapalene gel via the topical route.*" Only in this way can adequate labeling be developed to explain to prescribers the potential risks of higher systemic exposure of the 0.3% formulation which may impact teratogenic risks. This study could also verify the Study RD.03.SRE.2690 finding that showed that female subjects had higher adapalene exposures than male subjects. This study should also be included as a post-marketing commitment by the applicant.

1.2 Recommendation on Postmarketing Actions

Risk management for this new concentration could be addressed primarily through changes in labeling. More concise information regarding the risks involved with women of child bearing potential and potential teratogenic consequences with use of the product during pregnancy will be complete with the additional information obtained from studying the levels of systemic exposure of the two concentrations. Addition of currently available pregnancy outcome data to the label will enable prescribers to more fully inform patients of potential risks with pregnancy.

[ ]

1.2.2 Required Phase 4 Commitments

If this application is approved in this review cycle, the applicant should conduct a phase 4 study to compare the systemic exposure of Differin gel 0.1% and 0.3% under the "maximal usage conditions" (i.e., with a dose that would cover as large a body surface area as possible of the diseased skin), using the sensitive analytical method (LOQ $\leq$ 0.1 ng/mL).

Continued monitoring and reporting of adapalene exposed pregnancies[ ] should be negotiated with the applicant as a post-marketing commitment.

1.3 Summary of Clinical Findings

Differin (adapalene), 0.1%, a synthetic retinoid, is approved as a once daily topical treatment of acne vulgaris in patients 12 years of age and older, as a 0.1% solution (NDA 20-338, since discontinued) and gel (NDA 20-380) since 5/31/1996, and as a 0.1% cream (NDA 20-748) since 5/26/2000.

A New Drug Application (NDA) was submitted April 1, 2004 for adapalene gel, 0.3% under NDA 21-753.

The Division's action on February 1, 2005 was a non-approvable letter listing two deficiencies:

1. The pivotal study failed to demonstrate statistical superiority of the 0.3% adapalene gel over Differin (adapalene) Gel, 0.1%. Therefore, there is insufficient information to support the increased risk of the higher concentration.

2. The higher concentration of adapalene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%.

The applicant was requested to provide the following information to address the deficiencies:

1. Adequate evidence that the higher concentration of adapalene gel offers benefit over the currently available concentration of adapalene gel when used in the treatment of acne vulgaris (i.e., a comparative clinical study).

2. A risk management program (e.g., adequate labeling) to address the increased potential for teratogenicity given the systemic levels of adapalene seen in the submitted pharmacokinetic study."

The applicant has addressed these deficiencies in the intervening period in a series of meetings and teleconferences with the Agency.

Following a teleconference on April 13, 2005, and a guidance meeting on October 12, 2005, concurrence was reached on the first issue regarding statistical superiority, despite reservations from the Biostatistics team about the robustness of the data and the GEE analysis. The Division noted that "the efficacy benefit of the 0.3% product appears to be minimally greater than that of the 0.1%, but with a notable increase in potential teratogenic risk. Approval of such a product is dependent on a demonstration that the benefit outweighs the risk which may not be evident for Differin 0.3%".

The applicant, in a letter dated May 11, 2006, submitted their reasoning and pregnancy exposure data to refute the Division's prior conclusion that the 0.3% product [ ] [ ] Following internal review and consultation with the Agency Pregnancy and Maternal Health Staff, and the Division of Drug Risk Evaluation of the Office of Surveillance and Epidemiology, it was concluded that pregnancy category C is acceptable for both the adapalene 0.1% and 0.3% formulations with labeling that addresses the concerns of systemic exposure and teratogenic risk.

This reviewer does not disagree with the pregnancy category C based on the currently available information. The suggested maximal use pharmacokinetic systemic exposure data will more fully inform labeling.

1.3.1 Brief Overview of Clinical Program

The applicant conducted one Phase 3, safety and efficacy study (RD.06.SRE.18081) to demonstrate superiority to Differin, Gel, 1%, and to vehicle.

The applicant has also conducted other safety and efficacy studies, as follows:

- RD.03.SRE.2673, a European Phase 3 study comparing the 0.3% formulation against an EU formulation of adapalene gel 0.1%, different from the comparator used in the US Phase 3 trial, and without a vehicle arm. Safety was not assessed in the same way as the US pivotal trial.
- RD.SRE.18060, a Phase 2 dose comparison study, in which efficacy was assessed in a different way from the Phase 3 trial.
- RD.06.SRE1.18062, a long term Phase 3 open trial to assess safety and which was interrupted early on. Efficacy was assessed without comparators.

Topical safety studies conducted by the applicant, and which will be reviewed here, include:

- RD.03.SRE.2644, a cumulative irritancy study
- RD.03.SRE.2645, a photo-allergy study
- RD.03.SRE.2646, a phototoxicity study
- RD.03.SRE.2017, a topical sensitization study

These studies were reviewed in the initial review cycle and described in the clinical review by Dr. Joseph Porres dated January 19, 2005.

1.3.2 Efficacy

In the Phase 2 trial (RD.06.SRE.18060) adapalene gel, 0.3%, was superior to the 0.1% formulation only for non-inflammatory lesions and it failed to prove superiority to vehicle for inflammatory lesions.

In the Phase 3 pivotal trial (RD.06.SRE.18081), a total of 653 subjects were randomized (258 to adapalene gel, 0.3%, 261 to adapalene gel, 0.1%, and 134 to vehicle). There were no statistically significant differences in the ITT population groups with respect to demographic and baseline characteristics. The trial was multi-centered, randomized, double-blind, adequate and well controlled.

Co-primary efficacy endpoints included success rate, based on the Investigator's Static Global Assessment dichotomized to success and failure; and percent reduction in lesion counts (total, inflammatory and non-inflammatory).

The primary analysis for lesion counts was based on the pre-specified correlated repeated measurements at week 8 and week 12. Generalized Estimating Equation (GEE) methodology was used as the primary analysis.

The Agency determined in the initial review that there was not a statistically significant demonstration of superiority of the 0.3% formulation over the 0.1% formulation for the efficacy of the ITT population. In addition, no additional clinical benefit was determined from the higher concentration since there was the potential for greater systemic absorption leading to greater clinical risk and the potential for increased local safety effects leading to greater clinical risk.

Concurrence was reached on statistical superiority after an extensive review of post-hoc sensitivity analyses and review of differing interpretations of imputed missing data. The sponsor's efficacy data was found to be sensitive to how dropouts were handled. Despite reservations about the robustness of the data from the Biostatistics reviewers, the Division agreed that statistical superiority of 0.3% adapalene gel over 0.1% was demonstrated at the October, 2005 guidance meeting.

Agency analysis of change and percent change of inflammatory, non-inflammatory, and total lesions, although marginally in favor of the 0.3% gel, do not reach statistical significance. Analysis of the ITT population with last observation carried forward shows that none of the comparisons for lesion counts reach statistical significance for the 0.3% compared with 0.1% gel whether change, percent change or ranks is analyzed.

While the Agency conceded at the October, 2005 meeting that the minimal standard for significance using the GEE analysis had been reached, it was also noted that "the efficacy benefit of the 0.3% product appears to be minimally greater than that of the 0.1%, but with a notable increase in potential teratogenic risk. Approval of such a product is dependent on a demonstration that the benefit outweighs the risk which may not be evident for Differin 0.3%".

1.3.3 Safety

The total of healthy and diseased subjects reported to have received any adapalene 0.3% product is 2060 subjects. 430 healthy subjects and 1197 subjects with acne vulgaris received adapalene 0.3% gel; 64 subjects with plaque psoriasis, actinic keratosis, and keratoses/actinic lentigo received adapalene gel 0.3%. 337 healthy subjects and 8 subjects with photo-damaged skin received adapalene cream 0.3%. An additional 24 healthy subjects received adapalene solution 0.3%.

Four new studies of adapalene 0.3% have been conducted since the previous safety update submitted to the NDA in the initial review cycle. No deaths or serious adverse events were seen in the four new studies submitted in the safety update of the current complete response submission. Common adverse events were almost always mild, local, dermatologic reactions which resolved without specific therapy.

Applicant's Complete Response of December 18, 2006—Deficiency 2: Pregnancy Category and Teratogenicity:

The second deficiency in the non-approvable letter concerned the systemic levels of adapalene seen in the pharmacokinetic study and the potential for teratogenicity in exposed patients.

The original approval of the 0.1% topical formulations included assessment of systemic exposure using an assay less sensitive than that used for the assessment of the 0.3% formulation (LOQ of 0.35 ng/mL versus LOQ of 0.1 ng/mL, respectively). The Biopharmaceutics review found that when 2g of adapalene gel was applied to acne patients, 0.3% gel resulted in higher systemic exposure than the 0.1% gel (historical data) even when the difference in the sensitivity of the analytical methods used was considered.

A direct comparison of the two concentrations was not performed by the sponsor using the more sensitive assay, therefore, the data reported from submitted studies indicate that the 0.1% formulations have no systemic absorption, and the 0.3% formulation has a C_{max} of 0.55 ± 0.47 ng/mL and $AUC_{0\text{-}24hr}$ 8.4 ± 8.5 ng*h/mL.

A separate issue from the 4/13/05 teleconference as well as the 10/12/05 guidance meeting was the result from the PK study RD.03.SRE.2690 that showed that female subjects had higher adapalene exposures than male subjects. In this PK study, mean C_{max} and AUC (0-24) for females were ~100% and 150% higher than those for males, respectively.

In response to these concerns, the sponsor submitted a report that summarized worldwide pregnancy exposures to all adapalene exposures from spontaneous reports and clinical trials.

After review of these data, and in consultation with the Division of Drug Risk Evaluation in the Office of Surveillance and Epidemiology and the Pediatric and Maternal Health Staff, the Agency determined that a pregnancy category C with labeling enhancements would be recommended upon approval to address the second deficiency of the non-approvable letter.

This reviewer contends that the direct comparison of the systemic exposure of the two concentrations is essential to adequately inform the risks of the 0.3% gel with the minimal efficacy benefit that is alleged for the new product. In addition, the applicant has never addressed the differences in systemic exposure between female and male subjects seen in the pharmacokinetic study RD.03.SRE.2690. Since teratogenicity is the most prevalent

concern for the 0.3% gel, it would be important to know if this PK finding could be replicated and a rationale presented to explain it and its implications for exposed pregnancies.

1.3.4 Dosing Regimen and Administration

The applicant recommends treatment with adapalene gel, 0.3%, to be once daily at night.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Adapalene is a napthoic acid derivative with retinoid-like activity which has demonstrated efficacy in the treatment of acne vulgaris. The Applicant's proposed indication is for the once nightly, topical treatment of acne vulgaris in patients 12 years old and older.

Adapalene is approved for the topical treatment of acne and has been marketed by Galderma as a 0.1% solution (NDA 20-338), now discontinued, and gel (NDA 20-380) since 5/31/1996, and as a 0.1% cream (NDA 20-748) since 5/26/2000. This application is for a new dosage form, 0.3% gel, and the proposed trade name is Differin Gel 0.3%.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Pharmacology/Toxicology

Reproductive toxicology: In an oral reproductive performance and fertility study where F_0 female rats were treated with daily doses of 1.5, 5, or 20mg adapalene/kg for 15 days prior to pairing and throughout the gestation and lactation periods, no effects on reproductive

performance and fertility, F_1 litter size, growth, development to weaning, and subsequent reproductive performance of the offspring, were observed.

In dermal teratology studies with adapalene gels (0.03, 0.1, and 0.3%), the number of ribs in rats and rabbits at the highest dose (6mg/kg/day) level were increased. There were slight increases in the incidence of pre-sacral vertebrae (rabbit), asymmetric pelvis (rat) and small additional fissure in the parietal bone (rat), or more varied anomalies of the interparietal bone (rabbit).

In the oral teratogenicity study in rats (5, 25, and 60mg/kg/day), based on significant skeletal and visceral malformations both mid and high doses were established as teratogenic. At the low dose, only minimal skeletal variations (additional ribs) were observed. This dose was considered to be non-teratogenic, and this information appears in current labeling for the 0.1% formulations.

Adapalene has been shown to be teratogenic when administered orally to rats and rabbits at doses of 25 mg/kg/day and above (33 times the maximum recommended human dose (MRHD) for rats or 65 times MRHD for rabbits based on mg/m^2 comparisons). No teratogenic effect was seen in rats at an oral dose of 5.0 mg/kg/day adapalene (7 times the MRHD). Cutaneous teratology studies in rats and rabbits at doses of 0.6, 2.0, and 6.0 3 mg/kg/day (8 times the MRHD for rats or 16 times the MRHD for rabbits) exhibited minimal increases in supernumerary ribs in rats but no fetotoxicity. There are no adequate and well-controlled studies in pregnant woman.

The primary Pharm/Tox reviewer (Dr. Mainigi) recommended approval of the 0.3% formulation with pregnancy category C as was the category for the 0.1% approved gel formulation. The Pharm/Tox team leader (Dr. Brown) recommended [redacted] No new animal data was submitted in the complete response.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

No new clinical efficacy studies are provided in the complete response submission dated December 18, 2006. Please see the clinical review for the initial review cycle by Dr. Joseph Porres dated January 19, 2005 for a complete discussion of the clinical studies submitted during the initial review which resulted in a non-approvable action.

5. CLINICAL PHARMACOLOGY

No new data is provided in the current complete response submission. The original review concluded that increase in systemic exposure from 0.3% gel would result in greater systemic risk.

5.1 Pharmacokinetics

A more sensitive analytical method with an LOQ of 0.1 ng/mL was used in the PK study for the 0.3% gel that allowed for the estimation of systemic exposure of adapalene (C_{max} 0.55 ± 0.47 ng/mL and $AUC_{0\text{-}24hr}$ 8.4 ± 8.5 ng*h/mL, N=15) via the topical route. The studies performed for the 0.1% formulations was less sensitive (LOQ of 0.35 ng/mL) and demonstrated no systemic levels.

The following are the major conclusions of PK assessment:

a. When 2g of adapalene gel was applied to acne patients, 0.3% gel resulted in higher systemic exposure than the 0.1% gel (historical data) even when the difference in the sensitivity of the analytical methods used were considered.
b. 2g (that covers 6% body surface area) may not represent the maximal usage conditions, i.e., patients could use more than 2 g in the clinical setting. If a more than 2 g of adapalene gel (0.3%) dose is used, the exposure of adapalene could be higher than what was obtained in the current PK study.*
c. If a larger than 2 g dose is expected to be used in patients (for patients with >6% BSA), additional PK studies that enroll patients with larger body surface areas may be necessary to link safety to adapalene exposure.

This reviewer supports the recommendation of the Biopharmaceutics team that a pharmacokinetic study comparing systemic absorption of the 0.1 % and 0.3% gels under maximal use conditions, using the newer, and more sensitive analytical method *(LOQ ≤ 0.1 ng/mL)* should be performed as recommended at the April 13, 2005 teleconference.

A separate issue from that 4/13/05 T-con as well as the 10/12/05 meeting was the result from the PK study RD.03.SRE.2690 that showed that female subjects had higher adapalene exposures than male subjects. In this PK study, mean C_{max} and AUC (0-24) for females were ~100% and 150% higher than those for males, respectively. This additional issue for

increased teratogenicity does not seem to have been addressed by the sponsor in subsequent communications.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication is for the topical treatment of acne vulgaris

6.1.2 General Discussion of Endpoints

Please refer to the clinical review by Dr. Joseph Porres dated January 19, 2005.

6.1.3 Study Design

Please refer to the clinical review by Dr. Joseph Porres dated January 19, 2005.

6.1.4 Efficacy Findings

The conclusion of the clinical review during the initial review cycle was that the 0.3% formulation failed to demonstrate superiority over the 0.1% formulation for the ITT formulation on IGA and two lesion counts. These results paralleled the PP group. Although the 0.3% formulation was slightly more efficacious than the 0.1% formulation, it was also more irritating. In conclusion, there did not appear to be a significant advantage to the 0.3% formulation to support its approval.

Following a teleconference on April 13, 2005, and a guidance meeting on October 12, 2005, concurrence was reached on statistical superiority, despite reservations from the Biostatistics team about the robustness of the data and the GEE analysis. The Division noted that "the efficacy benefit of the 0.3% product appears to be minimally greater than that of the 0.1%, but with a notable increase in potential teratogenic risk. Approval of such a product is dependent on a demonstration that the benefit outweighs the risk which may not be evident for Differin 0.3%".

In the complete response submission currently under review, no further statistical information is provided, only a restatement of the October, 2005 meeting minutes. Particular attention should be paid to the last sentence referenced above from that meeting:

> *Approval of such a product is dependent on a demonstration that the benefit outweighs the risk which may not be evident for Differin 0.3%".*

The Biostatistical Team Leader Secondary Review dated February 5, 2007 contends "The results of this analysis show that the 0.3 % is superior to the 0.1% for the co-primary endpoint of success on the Investigator Global Assessment (IGA). However, analysis results of change and percent change of inflammatory, non-inflammatory and total lesions, although marginally in favor of the 0.3% do not reach statistical significance. Analysis based on ranks results in the following p-values (0.02, 0.02 and 0.06) for the comparison of inflammatory, non-inflammatory and total lesions. An analysis based on the ITT population with last observation-carried-forward shows that none of the comparisons for lesion counts (inflammatory, non-inflammatory and total lesions) reach statistical significance for the 0.3% vs. the 0.1% (whether one analyzes change, percent change or ranks).

Thus, while the pre-specified GEE methodology, which deals with observed cases and has issues with dropouts, met statistical significance, other types of analyses by the Agency question any level of efficacy. The level of efficacy must be minimal since several other measures of significance fail to document any benefit from Differin 0.3% gel.

The statistical recommendation is to present only week 12 efficacy results for labeling for consistency with labeling of other drugs for acne.

6.1.6 Efficacy Conclusions

The efficacy benefit of the 0.3% product appears to be minimally greater than that of the 0.1% adapalene gel. The applicant has satisfied the requirements of the February 1, 2005 non-approvable letter deficiency regarding statistical superiority by providing "adequate evidence that the higher concentration of adapalene gel offers benefit over the currently

available concentration of adapalene gel when used in the treatment of acne vulgaris (i.e., a comparative clinical study)."

This reviewer concurs with the statistical team recommendation to present only week 12 efficacy results in labeling for consistency with labeling of other acne drugs.

Reviewer comment: Given the lack of consistent statistical significance for efficacy with various analyses of the submitted data, GEE analyses may not be the appropriate mechanism to analyze data for future acne protocols. While GEE analysis was prespecified and agreed to with the Agency, the efficacy for this product is minimally, if at all, greater than the currently approved Differin gel product which has less systemic absorption.

7. INTEGRATED REVIEW OF SAFETY

In May, 2006, the applicant submitted pregnancy outcome data in adapalene exposed women to demonstrate the lack of teratogenic effects and the absence of retinoid embryopathy in those pregnancies.

The Complete Response submission dated December 18, 2006 contains a Safety Update for the period June 1, 2004-October 20, 2006. Four new studies have been performed with adapalene gel 0.3% and will be described in this review. Three are dermal safety studies comparing adapalene 0.3% to other topical retinoids, and one is a controlled efficacy and safety study comparing adapalene gel 0.3% gel to tazarotene gel 0.1% in the treatment of acne vulgaris. All four are listed as post-market support studies and detailed efficacy data are not submitted in support of labeling claims.

The Safety Update submitted December 18, 2006 also includes information on 10 new studies using adapalene gel 0.1% alone or in fixed combinations with other topical acne therapies. These are presented to add to the safety database for adapalene. They are discussed in Section 7.2.9, *Additional Submissions, Including Safety Update.*

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths reported during the conduct of any of the four new studies with adapalene gel 0.3%.

7.1.2 Other Serious Adverse Events

There were no serious adverse events reported during the conduct of any of the four new studies with adapalene gel 0.3%.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Five subjects discontinued a study prior to completion due to an adverse event. Two subjects complained of facial skin itching, one complained of eyelid erythema, one complained of periorbital facial swelling, and one complained of severe skin dryness along her jaw lines. All symptoms resolved with no residual effects. The relationship to study drug was judged as "possible" for all five cases.

Table 1
Subjects Discontinued Due to an Adverse Event
Adapalene Gel 0.1%

Study No	Subject No	Age/ Gender	Treatment	AE Diagnosis	Preferred Term	Outcome	Relationship To Study Drug	Serious	Subject Discont. Due to AE
29047	2[illegible]	50/F	Adapalene 0.3%	Itching on left side of face	Pruritus	Resolved, no residual effects	Possible	No	Yes

Study No	Subject No	Age/ Gender	Treatment	AE Diagnosis	Preferred Term	Outcome	Relationship To Study Drug	Serious	Subject Discont. Due to AE
29048	4	45/F	Adapalene 0.3%	Red irritated upper left eyelid	Erythema of eyelid	Resolved, no residual effects	Possible	No	Yes
29048	4	46/F	Adapalene 0.3%	Swelling of skin surrounding left eye	Swelling face	Resolved, no residual effects	Possible	No	Yes
29048	15	26/F	Adapalene 0.3%	Itching of facial skin around L eye and L corner of mouth	Pruritus	Resolved, no residual effects	Possible	No	Yes

Study No	Subject No	Age/ Gender	Treatment	AE Diagnosis	Preferred Term	Outcome	Relationship To Study Drug	Serious	Subject Discont. Due to AE
29048	091	18/F	Adapalene 0.3%	Facial dryness on bilateral jaw line	Dry skin	Resolved, no residual effects	Possible	No	Yes

7.1.5 Common Adverse Events

Initial Review Cycle 2004-2005

During the initial review cycle, the applicant reported 1505 subjects that were exposed to adapalene 0.3% products. Of these, there were 1,441 exposed to adapalene gel, 0.3%: 330 healthy subjects in the Phase 1 clinical pharmacology studies, and 1,111 subjects with *acne vulgaris* in the Phase 1 pharmacokinetic, Phase 2, and Phase 3 studies.

The applicant stated there was no evidence of sensitization, photosensitization, or phototoxicity from adapalene gel, 0.3%. In the irritancy study, adapalene gel, 0.3%, was similar to adapalene gel, 0.1%, and both were slightly more irritating than vehicle and White Petrolatum.

In the pivotal Phase 3 study (RD.06.SRE.18081) study, erythema, scaliness, and dryness, were more common for adapalene gel, 0.3%, than for the 0.1% formulation, and least for the vehicle, symptoms being generally mild, developed early in the treatment and decreased with continued treatment.

The more frequent AEs were local, dermatological reactions. Those considered treatment-related were more frequent in the adapalene gel, 0.3% and 0.1% groups (26.7% and 16.1% of subjects, respectively) than in the vehicle group (9.0%). Only 4 subjects (all in the 0.3% group) had non-dermatological, treatment- related AEs: facial edema, pain, keratoconjunctivitis, and eye pain. Other non-cutaneous AEs were infrequent and mild.

No deaths were reported during the development program for adapalene gel, 0.3%. No serious treatment-related AEs were reported during these studies. There were no mean changes in any hematology, blood chemistries, and urinalysis laboratory results that suggested a systemic effect of study drug.

Safety Update—June, 2004-October, 2006

The Complete Response submission dated December 18, 2006 contains a Safety Update for the period June 1, 2004-October 20, 2006. Four new studies have been performed with adapalene gel 0.3% and will be described in this section. Three are dermal safety studies comparing adapalene 0.3% to other topical retinoids, and one is a controlled efficacy and safety study comparing adapalene gel 0.3% gel to tazarotene gel 0.1% in the treatment of acne vulgaris. All four are listed as post-market support studies and detailed efficacy data are not submitted in support of labeling claims.

3 dermal safety studies (29049, 29047, and 29048) are submitted in addition to one phase 3b controlled efficacy and safety study (29045). The dermal safety studies compare adapalene gel 3% to either Tazorac (tazarotene) cream 0.05%, or Retin A Micro Gel 0.04% or Retin A Cream 0.05%, or some combination thereof.

186 subjects received adapalene gel 0.3% in the four new studies in the safety update. 20 (10.8%) subjects reported a total of 23 treatment related adverse events from the four new studies were attributed to the topical application of adapalene gel 0.3%. All were local dermatologic effects. 16 were pruritus, 2 reports of skin irritation, 2 reports of skin acne lesion breakouts, and 1 report each of dry skin, edema, and eyelid erythema.

Study 29049 reported no adverse events during the course of the study.

Study 29047 reported 6 subjects with adverse events. Five were pruritus, and one was a breakout of lesions on the face in a 67 year old woman.

Study 29048 reported 11 subjects experienced 14 adverse events related to adapalene gel 0.3%. 11 of these reports were itching at application sites, 1 report of eyelid swelling, 1 report of breakout of pimples on the chin application site, and 1 report of swelling around the left eye.

Study 29045 is a market support study conducted as a randomized, active control, multi-center, investigator blinded, parallel group protocol comparing adapalene gel 0.3% gel to tazarotene gel 0.1% in the treatment of acne vulgaris. 27 subjects (31.4 %) experienced 50 adverse events in the adapalene gel 0.3% group. 3 reports are felt to be related to adapalene treatment: 1 report of dry skin and 2 reports of skin irritation.

The signs and symptoms of skin irritation (erythema, scaling, dryness, and stinging/burning) with adapalene gel 0.3% were prospectively defined and assessed at baseline and at each post baseline visit in the pivotal phase 3 trial 18081, the long term, open label safety study 18082, (both previously reviewed with the original NDA submission) and in the new phase 3b efficacy study 29045. These were assessed distinctly from the adverse events listed above and were pre-specified in the protocols.

The percentage of subjects with mild erythema and mild stinging/burning were slightly higher in the new phase 3b study 29045 compared to the two studies previously reported in the original NDA. Subjects reported signs and symptoms of local skin irritation increased early in the treatment period, reaching maximums during the first week and decreased thereafter. They are listed in the following table:

7.1.5.4 Common adverse event tables

Table 3
Frequent Treatment Related Adverse Events
Adapalene Gel 0.3%

Most Frequently Reported (≥ 1%) Treatment Related Adverse Events

Treatment Group	RD.06.SRE.18081 Adapalene Gel, 0.3% N (%)	RD.06.SRE.18060 Adapalene Gel, 0.3% N (%)	SD.03.SRE.2673 Adapalene Gel, 0.3% N (%)	RD.06.SRE.29045 Adapalene Gel, 0.3% N (%)
Number of Subjects	269	70	269	86
Total Number of Related[1] Adverse Event(s)	82	60	71	5
Total No. (%) of Subjects with Related[1] Adverse Event(s)	57 (22.1%)	28 (40.0%)	83 (30.9%)	3 (3.5%)
Skin and Appendages	63 (21.3%)	28 (40.0%)	83 (30.9%)	3 (3.5%)
Skin dry	38 (14.0%)	16 (22.9%)	7 (2.4%)	1 (1.2%)
Discomfort skin	16 (5.9%)	8 (11.4%)	1 (0.5%)	0 (0.0%)
Erythema	2 (0.8%)	8 (11.4%)	3 (1.1%)	0 (0.0%)
Desquamation	4 (1.8%)	6 (8.6%)	0 (0.0%)	0 (0.0%)
Pruritus	6 (1.5%)	2 (2.9%)	1 (0.4%)	0 (0.0%)
Stinging	3 (1.2%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Irritant Dermatitis	2 (0.8%)	2 (2.9%)	46 (22.1%)	0 (0.0%)
Dermatitis	1 (0.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Dermatitis - contact	0 (0.0%)	1 (1.4%)	1 (0.6%)	0 (0.0%)
Infection	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Eczema	0 (0.0%)	0 (0.0%)	3 (1.4%)	0 (0.0%)
Atopic Dermatitis	0 (0.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)
Skin Irritation	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.3%)

[1] Related = Possibly, probably, or definitely related as determined by the Investigator

Study 18081 is the pivotal phase 3 trial; Study 18060 is the phase 2 safety and efficacy trial; Study 2673 is the phase 3 European long term safety and efficacy study (all 3 previously reviewed in the initial review cycle); and the newly submitted 29045 phase 3b study.

7.1.7 Laboratory Findings

The initial NDA review concluded that "*there were no patterns of clinically important laboratory changes indicative of a toxic effect following up to 12 months of treatment with adapalene gel, 0.3%. No trends or patterns in laboratory parameters were observed that were indicative of toxicity in the short-term controlled studies or the long-term study.*"

No new laboratory data are presented in the four new studies with adapalene 0.3% gel presented in the safety update.

7.1.14 Human Reproduction and Pregnancy Data

The applicant submitted in May, 2006, a report detailing adapalene exposed pregnancy data to comply with the second deficiency in the February 1, 2005 non-approval letter that "The higher concentration of adapalene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%." The

Agency requested "A risk management program (e.g., adequate labeling) to address the increased potential for teratogenicity given the systemic levels of adapalene seen in the submitted pharmacokinetic study."

The applicant stated that since the launch of adapalene 0.1% in September, 1995, approximately [ ] patients have been exposed to adapalene, of which 64% were female patients. 156 pregnancies have been reported through March, 2006. Though adapalene 0.3% is not yet marketed in any country, 6 patients reported pregnancies while exposed to the 0.3% formulation. One additional patient received several formulations (0.05%, 0.2%, and 0.3% during an adapalene clinical trial.

Of these 163 pregnancies, 55 were lost to follow up, 11 were ongoing at the time of the report, and 97 (59%) had a known outcome. 68 of the 97 had a "normal" outcome (details were not provided); 10 cases ended with spontaneous abortion, 10 cases with elective abortion, and congenital abnormalities in 6 cases. One case was a premature baby's death (gestational age not reported), one case was a fetal death following placental abruption, and one case ended with an ectopic pregnancy.

Data for the proposed 0.3% adapalene gel product included 7 pregnancies, of which 6 had a known outcome. 4 healthy babies and 2 elective abortions were reported in this group.

Six cases of congenital abnormalities were included in this submission, of which five were previously known to the Agency. All of these cases were associated with the adapalene 0.1% formulations. Three of the five cases were considered potential cases of retinoid-specific, adapalene associated teratogenicity. The sixth new case occurred in a young woman who used both adapalene 0.1% and topical clindamycin during the first two weeks of her pregnancy. This case described multiple organ system anomalies, including Dandy Walker malformation and scimitar syndrome which were not consistent with the overall picture of retinoid abnormalities.

The sponsor states that the congenital malformations reported in 6 cases are not typical for retinoid malformations described in the literature.

The Division of Drug Risk Evaluation (DDRE) of the Office of Surveillance and Epidemiology (OSE) previously analyzed AERS post-marketing reports of pregnancy exposure with adapalene 0.1% in May, 2004. From the AERS data alone, they concluded that a compelling safety signal for retinoid specific birth defects was not identified.

The DDRE review of September 8, 2006 agrees with this principle conclusion, stating "Based on our previous analysis and the additional information provided in the sponsor's submission, DDRE does not find a compelling safety signal for retinoid-specific birth defects associated with topical adapalene use from the AERS reports alone"

The Pregnancy and Maternal Health Staff (PMHS) was consulted regarding the pregnancy labeling for adapalene 0.3 % gel. Their conclusion, dated October 11, 2006, is as follows:

> Based on the lack of additional animal data, low systemic exposure and no compelling evidence of teratogenicity of the 0.1% topical formulations, the *PMHS recommends no change in the pregnancy category if the adapalene 0.3% topical gel is approved.* Using different pregnancy categories for topical formulations of the same product may lead to prescriber and user confusion. Having the 0.1% gel and cream labeled as a category C and the 0.3% gel labeled as a category[ ] implies that we have reviewed more data than we have actually reviewed.

Dr. Sandra Kweder added to the PMHS review on July 27, 2006, "Recommend label include information about reports of pregnancy exposures if it can be brief."

After internal review, the Agency communicated to the applicant on September 12, 2006, that "With modified labeling, the Agency is agreeable to a Pregnancy Category of "C". The revised labeling will contain wording to address the Agency's concern that the increased systemic exposure, observed in Differin 0.3% formulation, could increase the teratogenic risk to patients."

Labeling negotiations with the applicant are ongoing as of the date of this clinical review.

7.1.17 Postmarketing Experience

Adapalene 0.3 % gel is registered in Canada but is not yet marketed. It has not been approved or marketed in any other country to date.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Please refer to the clinical review by Dr. Joseph Porres dated January 19, 2005.

7.2.9 Additional Submissions, Including Safety Update

The Safety Update submitted December 18, 2006 also includes information on 10 new studies using adapalene gel 0.1% alone or in fixed combinations with other topical acne therapies. These are presented to add to the safety database for adapalene.

One dermal safety study for post market support and one phase 2 efficacy and safety studies are included. Synopses and adverse event data are presented for 4 controlled efficacy and safety studies, one in Japan [redacted] and 3 for post market support. Data for 4 uncontrolled studies, one for long term safety conducted in Japan, and 3 for post-marketing support are also presented.

There were no deaths during the any of the reported studies with adapalene 0.1% gel.

There were 15 reports of a serious adverse event by 11 subjects enrolled in these studies. Only one subject discontinued therapy for a serious adverse event. This 27 year old woman was diagnosed with an ovarian cyst on routine periodic health examination and had completed 28 days of adapalene 0.1% therapy. The relationship of study drug to the event was judged by the investigator to be unlikely, and this reviewer concurs.

7 of the 11 subjects reporting serious adverse events experienced pregnancy. One experienced intrauterine fetal death and placental abruption. One experienced a spontaneous miscarriage at 13 weeks of pregnancy three weeks after study withdrawal at day 27 of treatment. One subject decided to electively terminate her pregnancy following 179 days of treatment. One subject became pregnant at 109 days of treatment and was diagnosed with a hemorrhagic ovarian cyst. She delivered a normal, healthy baby at term. One subject became pregnant at 59 days of application. She required a circumferential suture placement in her cervix which had been performed for cervical incompetence in two prior pregnancies. No report of the outcome of the pregnancy was provided. One subject was withdrawn at 295 days of therapy because of pregnancy. She developed placenta previa and was hospitalized due to bleeding. Uterine artery embolization was performed. No report of pregnancy outcome was reported. One subject withdrew at 59 days due to pregnancy. Eight months later she was hospitalized with herpes zoster. No pregnancy outcome is reported.

The other cases involved appendicitis, facial fracture, and attempted suicide.

The relationship of the study drug, adapalene 0.1%, seems unlikely to any of these serious adverse events.

19 additional subjects discontinued adapalene 0.1% therapy from adverse events not judged as serious. These included dermatitis, sunburn, skin discomfort or irritation, eczema, acne flares that were likely related to topical therapy and are appropriately labeled for such reactions. Other conditions reported were tachycardia, sore throat, ovarian cyst, headache,

nausea, vomiting, sinusitis, and vertigo. None of these were judged by the investigator or this reviewer as related to study medication.

In study 27006, a phase 3 uncontrolled long term safety study conducted in Japan, one 27 year old male subject developed elevated ALT, AST, and GGT levels. Two subjects had increased total bilirubin. All outcomes are reported as "continuing" and the relationship to study drug as "possible". In the original NDA review by Dr. Porres, no mean changes in laboratory parameters were noted and no systemic effect was reported. One subject in the original NDA submission had elevated liver enzymes.

Four of the studies utilized adapalene 0.1% gel in fixed combination with benzoyl peroxide 2.5% gel. 7 serious adverse events were reported by 6 subjects in these studies. These reports were substance abuse, syncope, staphylococcal infection of the leg, bipolar disorder, depression, and clavicle fracture. None of these were judged by the investigator or this reviewer as related to study medication.

11 subjects in this group discontinued adapalene 0.1% therapy due to adverse events not judged as serious. These included: impetigo, drug abuse, urticaria, dermatitis, worsening of acne, skin dryness, dermatitis, influenza and facial swelling. The dermatologic effects are likely due to study therapy but are previously reported and appropriately labeled.

The studies which include adapalene 0.1% gel use describe local dermatologic effects seen in previous studies. They include dry skin, erythema, pruritus, acne breakouts, skin desquamation, pain, and skin irritation. Again, the dermatologic local effects are likely due to study therapy but are previously reported and appropriately labeled in all the adapalene topical products.

Reviewer comment: This reviewer concurs with the safety assessment of the original NDA reviewer, Dr. Porres. He noted that local dermatologic effects of adapalene such as dryness, pruritus, peeling, and stinging/burning are expected adverse events with a topical retinoid. Adverse events leading to discontinuation are either known effects with adequate labeling or were unlikely to be related to study drug.

There is no information in the newly submitted adapalene 0.1% studies to warrant additional concerns for safety or substantial changes in product labeling.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant recommends the drug product be dosed once daily, at night, and this dosage is consistent for this type of drug product. The dosing has not changed from the original submission.

8.7 Postmarketing Risk Management Plan

If this application is approved in this review cycle, the applicant should conduct a phase 4 study to compare the systemic exposure of Differin gel 0.1% and 0.3% under the "maximal usage conditions" (i.e., with a dose that would cover as large a body surface area as possible of the diseased skin), using the sensitive analytical method (LOQ $\leq$ 0.1 ng/mL).

9. OVERALL ASSESSMENT

9.1 Conclusions

The applicant has addressed the deficiencies in the non-approvable letter from the initial review cycle. While the Agency conceded that the minimal statistical burden has been met for approval, there remain issues of potential teratogenic effects, gender differences in systemic exposure, and whether the minimal efficacy benefit outweighs the safety concerns expressed by the biopharmaceutics and pharmacology/toxicology reviews.

These issues can be addressed through the completion of a post-marketing pharmacokinetic study to compare systemic absorption of the 0.1 % and 0.3% gels under maximal use conditions, using the newer, more sensitive analytical method (LOQ $\leq$ 0.1 ng/mL).

No information is presented in the safety update to warrant additional concerns for safety or substantial changes in product labeling.

9.2 Recommendation on Regulatory Action

This reviewer recommends that Differin (adapalene) Gel, 0.3% be approved for the topical treatment of acne vulgaris in patients twelve years of age and older.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The completion of a post-marketing pharmacokinetic study to compare systemic absorption of the 0.1 % and 0.3% gels under maximal use conditions, using the newer, more sensitive analytical method (LOQ $\leq$ 0.1 ng/mL) should be negotiated with the applicant as a post-marketing commitment.

[ ] At a minimum, the applicant should be encouraged to continue to monitor adapalene exposed pregnancies from all concentrations in products worldwide and periodically report the outcomes of the exposed pregnancies to the Agency.

9.4 Labeling Review

Labeling discussions with the applicant are ongoing as of the date of this review.

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/s/

David Kettl
3/27/2007 09:22:04 AM
MEDICAL OFFICER

Markham Luke
4/25/2007 10:23:33 AM
MEDICAL OFFICER
See also consultation reply from Pregnancy Labeling Group. See also Clinical TL review.

Susan Walker
6/1/2007 12:59:57 PM
DIRECTOR

Clinical Team Leader Secondary Review
NDA 21-753 Differin (adapalene) Gel 0.3%

January 21, 2005

The regulatory recommendation for action for Differin (adapalene) Gel 0.3% for the treatment of acne vulgaris is based on a multi-disciplinary evaluation of this drug, its risks, and its benefits. The Clinical Team Leader agrees with the primary reviewer, Dr. Joseph Porres, regarding a recommendation for not approving this NDA. The Applicant failed to achieve its primary endpoint in the submitted clinical study. The one pivotal (dose ranging) study submitted failed to demonstrate statistical superiority of the 0.3% Differin gel over the 0.1% Differin gel. In addition, the higher concentration 0.3% topical drug product resulted in detectable serum concentrations and along with it, higher systemic teratogenic risk than with the currently approved 0.1% gel.

Drug Efficacy

The protocol for the one pivotal study pre-specified a Generalized Estimating Equation (GEE) methodology to allow for correlated repeated measurements at week 8 and week 12 to be factored in. The intent of such an analysis was to reduce the number of subjects and at the same time increase the number of observations. Despite the GEE evaluation, efficacy as determined by lesion counts did not demonstrate a significant benefit for the 0.3% gel over the 0.1% gel for the treatment of acne vulgaris.

The Biostatistics review, conducted by Dr. Valappil, concluded that the 0.3% gel failed to demonstrate superiority over the 0.1% gel for all three lesion counts (total, inflammatory, and non-inflammatory, % change, ITT, GEE analysis with respective p-values of 0.326, 0.164 and 0.560). However, with the intent-to-treat analysis with the last observation carried forward (ITT-LOCF), the 0.3% gel did demonstrate superiority over 0.1% in the Investigator's Global Assessment (IGA) with p=0.028. Unfortunately, demonstrating superiority only with the IGA is insufficient as a demonstration of superiority for the acne indication. In general, acne products need to be superior with regard to at least two out of three lesion counts (total, inflammatory, and non-inflammatory) and superior with regard to the IGA. Of note, the 0.1% arm did not demonstrate superiority over vehicle using the GEE analysis of the ITT population (p=0.42) in the submitted study.

The robustness of this analysis was demonstrated by several sensitivity analyses conducted by both the Biostatistics team and the Applicant. These sensitivity analyses (which included univariate analyses, absolute change, and rank) also failed to demonstrate statistical superiority of the 0.3% gel arm over the 0.1% gel arm (see Biostatistics review).

During the review, the team also attempted to evaluate whether the 0.3% gel was superior to gel vehicle with the supposition that superiority to vehicle in two studies

would be supportive of an approval action if there were no significant safety concerns with the higher concentration.

A post-hoc analysis (with no adjustments made for multiplicity) did demonstrate superiority of the 0.3% gel over gel vehicle for all of the co-primary endpoints. The 0.3% gel was superior in total, inflammatory, and non-inflammatory lesion counts (as per the same analysis as above [see page 16 of Biostatistics review] p = 0.001, 0.003, and 0.007 respectively). Additionally, the 0.3% gel was superior to the vehicle with the IGA with p = 0.010. However, with this post-marketing dose ranging study, a demonstration of some gain in benefit over the existing product would be needed to counter any demonstration of adverse safety for the higher dose (see Drug Safety below).

Drug Safety

The major concern is the detectable serum concentration with the higher concentration 0.3% topical drug product. Previous formulations of adapalene at 0.1% did not result in measurable serum levels of adapalene or metabolite.

As per the Biopharmaceutics review, the one in vivo PK study (RD.03.SRE.2690) was conducted in 16 patients with plasma adapalene measured on Day 10 after 2 grams per day application of the 0.3% gel. Adapalene was detectable in 15 out of 16 patients with a lower limit of quantitation (LOQ) of 0.1 ng/mL. Cmax on Day 10 was 0.553 +/- 0.466 ng/mL. The maximum Cmax was 2 ng/mL and was observed in a female subject. In general, the female subjects had higher adapalene exposure than male subjects. The Biopharmaceutics reviewer also stated that "It is noted that the patients in this study were not necessarily tested under the maximal usage condictions, i.e., they did not have as high a percentage of BSA of the disease skin as possible...The dose was, however, at the high end considering that mean daily dose used in the three 12 week Phase 2 and 3 studies was approximately 0.6 to 0.9 g/day." It should also be noted that with irritation (usually observed after Day 10) and compromise of the dermal barrier, there may be increased systemic absorption of the retinoid. Additionally, the previous pharmacokinetic studies with application of 2 g of 0.1% adapalene gel or cream to acne patients showed that serum levels of adapalene were not detectable with a LOQ of 0.35 ng/mL.

With this information on hand (Biopharmaceutics review completed on January 18, 2005), the Clinical and Pharmacology/Toxicology disciplines discussed that a

[redacted] Please see primary Clinical review by Dr. Porres and Pharm/Tox memo by Dr. Paul Brown. This significant increase in risk for this drug product would need to be balanced with sufficient benefit to allow for approval. Unfortunately, such a benefit was not seen in the comparative study submitted.

Local adverse events were also worse with the 0.3% gel than the 0.1% gel in the submitted clinical study. However, such worsening of local safety is potentially addressable in labeling and would not be a reason for an adverse approval action for this drug product.

Labeling and Product Name

Due to the recommendation for non-approval, labeling is not currently a relevant review issue. [ ] [ ] The Differin XP product name is not acceptable (as per DMETs review – XP for eXtra Potent).

Recommendation for Regulatory Action

It is recommended that this NDA not be approved due to lack of benefit to support the added risk of the higher concentration. Adequate evidence that the higher concentration of adapalene offers benefit over the currently available concentration of adapalene when used in the treatment of acne vulgaris is needed (i.e., a comparative clinical study). Further, a risk management program (e.g. adequate labeling) should be proposed to address the increased potential for teratogenicity given the systemic levels of the retinoid adapalene seen in the submitted pharmacokinetic study.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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/s/

Markham Luke
1/21/05 04:22:07 PM
MEDICAL OFFICER
Clinical TL secondary review.

Jonathan Wilkin
1/31/05 12:11:39 PM
MEDICAL OFFICER
Disagree with TL's assertion that "These sensitivity analyses...failed.." A least one sensitivity analysis did show superiority of the .3 v .1%, but that is insufficient evidence. otherwise agree with TL review.

Clinical Team Leader Secondary Review
NDA 21-753 Differin (adapalene) Gel 0.3%

June 5, 2007

Differin (adapalene) Gel is currently marketed in a 0.1% formulation. The original submission, NDA 21-753, for a 0.3% Gel received a Not Approval letter on February 1, 2005. A resubmission was received on December 18, 2006. The Clinical Team Leader concurs with the Primary Medical Review that on resubmission, the 0.3% gel be approved for the topical treatment of acne vulgaris in patients age 12 years and older. The major issues that received further evaluation on the second review cycle included the efficacy gained with the 0.3% formulation when compared to the lower concentration 0.1% formulation, systemic exposure and the unknown risk of teratogenicity with the higher concentration, and review of additional post-marketing information for the 0.1% formulation submitted by the sponsor.

Efficacy

As described in the previous Clinical Team Leader Secondary Review dated January 21, 2005, the Primary Statistical Review dated January 14, 2005, and the Biostatistics Team Leader Secondary Review dated February 5, 2007, the single clinical study with three arms demonstrated that the 0.3% arm was statistically superior to the 0.1% for the Investigator Global Assessment (IGA) co-primary endpoint using a repeated measures analysis, but "analysis results of change and percent change of inflammatory, non-inflammatory and total lesions, although marginally in favor of the 0.3%, do not reach statistical significance." The pre-specified analysis was the repeated measures, GEE analysis, results were described in the Primary Statistical Review:

> In the GEE analyses (Table 9) at multiple time points (Week 8 and Week 12), Adapalene Gel, 0.3% was superior to Adaplaene Gel, 0.1% (p=0.02) in IGA success rates. However, Adapalene 0.1% failed to show superiority over vehicle (p=0.41). In the analysis of the total lesion counts, Adapalene Gel, 0.3% failed to demonstrate superiority in percent reduction over Adapalene Gel, 0.1% (p=0.19). In the analysis of the inflammatory lesion counts, Adapalene Gel, 0.3% achieved a border-line significance in percent reduction over Adapalene Gel, 0.1% (p=0.05). In the analysis of the non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.49).

As discussed in the Statistical reviews, there was concern about the impact of the handling of dropouts in the sponsor analysis, so additional sensitivity analyses were requested by the Agency. The additional sensitivity analyses continued to show no statistical significance of the non-inflammatory and total lesions, although they were trending in favor of the 0.3% concentration vs. the 0.1% concentration.

Clinically, the point estimates of 21% week 12 success with the 0.3% vs. 16% week 12 success with the 0.1% and 9% with the vehicle gel, suggests a dose dependant response. In this active-controlled study, superiority of the 0.03% product to vehicle was clearly demonstrated with a p-value of 0.002. Only a modicum of benefit is demonstrated using GEE analysis for the comparison of the 0.3% product vs. the 0.1% product, with a p-value for the IGA comparison of 0.028.

Teratogenicity

The Not Approvable letter stated the following, "The higher concentration of adapalene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%."

The applicant, Galderma Laboratories, was asked to review the existing pregnancy database for the lower concentration 0.1% adapalene. On resubmission, Galderma provides information that the existing database for 0.1% did not have a higher rate of birth defects compared to background. Further, the Galderma assertion was supported by a review conducted by the Pediatric and Maternal Health Staff (PMHS) in the Office of New Drugs dated July 27, 2006, with a further correction dated October 11, 2006. The recommendation of that review was that "Based on the lack of additional animal data, low systemic exposure and no compelling evidence of teratogenicity of the 0.1% topical formulations, the PMHS recommends no change in the pregnancy category if the adapalene 0.3% topical gel is approved." Of note, there were literature reports of three cases of malformations after maternal use of the 0.1% formulation. However, the PMHS did not feel that these were compelling. These three cases were all reviewed by the Division of Drug Risk Evaluation in 2004, and at that time, the recommendation for the 0.1% adapalene label was that no change was needed for the label. The PMHS recommendation was also based on concern for potential for "prescriber and user confusion" if there were different labeled Pregnancy categories of [ ] and C for the 0.3% and 0.1% respectively.

With the current review cycle, the Pharmacology and Toxicology supervisory review dated June 1, 2007 provides wording for Pregnancy category C labeling. In addition, the following statement in the supervisory Pharmacology and Toxicology review is relevant:

> All pregnancies have a risk of birth defect, loss, or other adverse event regardless of drug exposure. Typically, estimates of increased fetal risk from drug exposure rely heavily on animal data. However, animal studies do not always predict effects in humans. Even if human data are available, such data may not be sufficient to determine whether there is an increased risk to the fetus. Drug effects on behavior, cognitive function, and fertility in the offspring are particularly difficult to assess.

The pharmacokinetic information regarding systemic blood levels submitted in the first review cycle indicated detectable levels of adapalene with the 0.3% formulation (see Clinical Biopharmaceutics review). [

[

] Given the PMHS review recommendation, based on a survey of the human data, a recommendation for Pregnancy Category C is supportable. However, the product should not be used in pregnant women and the wording in the label will reflect this. The submitted human data will also be included in the label:

> "In clinical trials involving DIFFERIN Gel, 0.3% in the treatment of acne vulgaris, women of child-bearing potential initiated treatment only after having had a negative pregnancy test and used effective birth control measures during therapy. However, 6 women treated with DIFFERIN Gel, 0.3% became pregnant. One patient elected to terminate the pregnancy, two patients delivered healthy babies by normal delivery, two patients delivered prematurely and the babies remained in intensive care until reaching a healthy state and one patient was lost to follow-up."

Thus, the additional risk of the higher concentration adapalene gel is not known, however, is thought to be relatively small. In addition, post-marketing information provided by Galderma regarding pregnancies with the 0.1% products indicate a relatively low teratogenic risk. Additional risk can be minimized through careful risk management, e.g. labeling and post-market surveillance. In assessing the current submission, the clinical review team has considered that the applicant has addressed risk management adequately with revisions to the previous first cycle draft of labeling. The Clinical Team Leader concurs with the Primary Clinical review that some form of post-marketing surveillance should be conducted. This does not have to be a registry, as such a registry for a topical product would be difficult and impractical to implement. Continued monitoring and reporting of adapalene exposed pregnancies by the applicant will be requested by the Agency.

In addition, as recommended in the Primary Clinical Review, the Agency requested from the applicant the following post-marketing commitment: "Conduct a post-marketing study to compare the systemic exposure with Differin Gel 0.1% and 0.3% under maximal usage conditions (i.e. with a dose that would cover as large a body surface area as possible of the diseased skin) using the most current sensitive analytical method. Submission of protocol was requested by October 1, 2007 and submission of the final study report by December 31, 2008." The results of this study will be used to inform labeling for both products.

Labeling:

Separate labeling for the 0.3% product was provided in the current submission. The separation of labeling is not an approvability issue; [redacted]

Conclusion:

In summary, based on the information submitted and the revised labeling for Differin in the response to the Not Approvable letter, the Clinical Team Leader recommends that Differin (adapalene) Gel, 0.3% be approved for the topical treatment of acne vulgaris in patients age 12 and older, with labeling that is agreed upon by the review team and the sponsor, and with the post-marketing commitment as recommended by the Clinical and Biopharmaceutics reviews.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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/s/

Markham Luke
6/12/2007 02:00:34 PM
MEDICAL OFFICER
TL secondary review

Susan Walker
6/20/2007 09:44:40 PM
DIRECTOR