CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-753

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 14, 2004

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Products
HFD-540

VIA: Mildred Wright, Regulatory Health Project Manager
Division of Dermatologic and Dental Products
HFD-540

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Differin XP (adapalene) Gel, 0.3%, NDA 21-753

Background and Summary

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Differin XP (adapalene) Gel, 0.3%, NDA 21-753. We have simplified the wording, made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on June 25, 2004. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

3 page(s) of draft labeling has been removed from this portion of the review.

DSRCS Review of Patient Labeling -12/14/04

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

/s/

Jeanine Best
12/14/04 10:02:40 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
12/14/04 12:07:19 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

Date: July 27, 2006

From: Lisa L. Mathis, M.D.

Through: Sandra Kweder, MD
Deputy Director, Office of New Drugs

To: David Kettl, MD
Mildred Wright
DDDP, ODE 3
Office of New Drugs

Subject: Differin (adapalene) gel, 0.3%

Date Consulted: June 12, 2006

Materials Reviewed: NDA 21-753

Consult Question: Differin (adapalene) 0.1% is indicated for the treatment of acne vulgaris and is a pregnancy category C. A NDA has been submitted for a 0.3% gel, and the Sponsor has been requested to initiate 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. There is a question regarding need to change pregnancy category based on higher systemic exposure of the 0.3% topical gel when compared to the 0.1% topical formulations.

- **EXECUTIVE SUMMARY**

Differin (adapelene), 0.1% 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) and gel (NDA 20-380) since 5/31/1996, and as a 0.1% cream (NDA20-748) since 5/26/2000. The 0.1% solution has been discontinued. A New drug Application (NDA) was submitted 1 April 2004 for adapelene gel, 0.3%, and while it has been established that there is clinical benefit of the increased concentration gel, there is still question regarding safety. The current labeling for the 0.1% topical formulations includes a pregnancy category C, but with the potential for increased systemic exposure from the use of the 0.3% gel, the Division of Dermatologic and Dental Products has question regarding the safety of this product in women who may become pregnant.

Adapalene is a synthetic analog of retinoic acid selectively binds to RARβ and –γ nuclear receptors of retinoic acid. Retinoids are known teratogens when there is significant systemic exposure. Retinoic Acid embryopathy consists of craniofacial, cardiovascular, and central nervous system defects as well as thymic and parathyroid abnormalities.

The original approval of the 0.1% topical formulations included assessment of systemic exposure using an assay with sensitivity lower 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). A direct comparison of the two concentrations was not performed by the Sponsor using the mores sensitive assay, therefore, the data we currently have from submitted studies indicates 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. Literature reports suggest that absorption of the 0.1% formulations is not zero, but it is less than that demonstrated with the 0.3% formulation. It should be noted that the clinical trials are fairly provocative as they approximated 6% BSA involvement, and clinical studies demonstrated that clinical use was less than half of that used in the systemic absorption studies.

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.

- **BACKGROUND**

Differin (adapelene), 0.1% 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) and gel (NDA 20-380) since 5/31/1996, and as a 0.1% cream (NDA20-748) since 5/26/2000. The 0.1% solution has been discontinued.

Adapalene is a synthetic analog of retinoic acid selectively binds to RARβ and –γ nuclear receptors of retinoic acid. Retinoids are known teratogens when there is significant systemic exposure. Retinoic Acid embryopathy consists of:

- Craniofacial defects that may include: facial asymmetry, microtia and/or anotia with stenosis of the external ear canal, posterior helical pits, facial nerve palsy ipsilateral to malformed ear, narrow sloping forehead, micrognathia, flat depressed nasal bridge, ocular hypertelorism, and mottling of teeth
- Cardiovascular defects that may include: conotruncal malformations, including transposition of the great vessels, tetralogy of Fallot, truncus arteriosus communis, supracristal ventricular septal defect, aortic arch interruption, retroesophageal subclavian artery, aortic arch hypoplasia, and hypoplastic left ventricle, and
- Central nervous system defects that may include: hydrocephalus, microcephaly, structural errors of cortical and cerebellar neuronal migration and gross malformations of posterior fossa structures),
- Subnormal range of intelligence, and
- Sometimes thymic and parathyroid abnormalities.

Current Labeling:
The CLINICAL PHARMACOLOGY section of labeling states the following:
"Pharmacokinetics: Absorption of adapalene from DIFFERIN® Cream through human skin is low. In a pharmacokinetic study with six acne patients treated once daily for 5 days with 2 grams of DIFFERIN® Cream applied to 1000 cm^2 of acne involved skin, there were no quantifiable amounts (limit of quantification = 0.35 ng/mL) of adapalene in the plasma samples from any patient. Excretion appears to be primarily by the biliary route."

The PRECAUTIONS section of labeling for the 0.1% adapelene topical formulations states the following:
"Pregnancy: **Teratogenic effects. Pregnancy Category C.** No teratogenic effects were seen in rats at oral doses of 0.15 to 5.0 mg/kg/day adapalene (up to 20 times the MRHD based on mg/m^2 comparisons). However, adapalene administered orally at doses of 25 mg/kg, (100 times the MRHD for rats or 200 times MRHD for rabbits) has been shown to be teratogenic. Cutaneous teratology studies in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day (24 times the MRHD for rats or 48 times the MRHD for rabbits) exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Additional Safety information:
A safety review was conducted May 19, 2004 by Division of Drug Risk Evaluation. A review of the AERS database and medical literature recovered three potential cases of retinoid specific, adapalene gel-associated teratogenicity (US 7/2003, Finland 1/2001, France 10/1996). One of these cases occurred in France and has been well described in the medical literature.[1,2] The other two cases include a domestic report provided by a consumer and an

[1] Autret E, Berjot M, Jonville-Bera AP, et al. Anopthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy (letter). Lancet 1997;350(9074):339

infant with pathology described only as "brain damage" from Finland. Postmarketing adverse event data did not suggest a compelling safety signal for retinoid-specific birth defects in association with topical adapalene and no changes to labeling were recommended.

Differin (adapelene) gel, 0.3%

A New drug Application (NDA) was submitted 1 April 2004 for adapelene gel, 0.3%. The action taken on this application 1 February 2005 was a nonapproval (NA) with the following deficiencies noted:

1. "The pivotal study failed to demonstrate statistical superiority of the 0.3% adapalene gel over Differin (adapelene) Gel, 0.1%. Therefore, there is insufficient information to support the increased risk of the higher concentration.
2. The higher concentration of adapelene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%."

The sponsor 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."

A guidance meeting was held 12 October 2005 to provide guidance on the two deficiencies listed in the NA letter. Concurrence was reached on point #1, that the 0.3 % formulation wins over the 0.1 % gel despite reservations about the robustness of the data from the Biostatics team. It was noted in the 10/12/05 minutes 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 dependant on a demonstration that the benefit outweighs the risk which may not be evident for Differin 0.3%."

The Clinical Pharmacology reviewer noted that "The Sponsor could conduct a study to compare the systemic exposure of 0.1% and 0.3% gel 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). The results from this study would 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." This recommendation was based on the fact that the initial approval of the adapelene 1% formulations was based on data using an analytical method with a LOQ of $\leq$0.35 ng/mL where no systemic exposure was noted. Also, the reviewers were concerned that the studies only enrolled patients who has approximately 5-6% BSA involvement when the estimated maximal BSA involvement may be >6% BSA. It should be noted that when one is using %BSA, a difference of 1% may not

[2] Birth defects due to topical adapalene and tretinoin. Prescrire Int 1998;7(37):148-9

be clinically relevant, especially given that in clinical trials, patients only used about 1 gram per day – meaning that the clinical %BSA involvement was closer to 3% BSA.

- **REVIEW OF DATA**

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 recommended approval with no change in pregnancy category for the 0.3% formulation. The pharm/tox reviewer recommended [redacted]

Clinical Pharmacology: Increase in systemic exposure from 0.3% gel would result in greater systemic risk. 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 perfrmed 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.

*It should be noted that the Sponsor evaluated systemic exposure of adapalene in patients following application of 2 g of adapalene 0.3%, gel per day to the diseased skin that covered a skin area of about 1000 cm_2 (~5-6% BSA) for 10 days. Although this dose did not represent that of patients with large BSA involvement (>6% BSA), the 2 g/day dose is clinically relevant 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. In actual use, the 2 grams would overestimate the actual usage condition exposure.

Literature reports:
There are a few literature reports of systemic exposure with adapalene 0.1% topical gel.[3] A liberation/penetration study demonstrated that significant quantities of adapalene were present in epidermis and dermis, but only 0.01% of the applied dose penetrated through the skin. [4]

Clinical Experience: Adapalene topical formulations, 0.1%, have been marketed worldwide since 1995. These products are approved for the treatment of acne vulgaris in 86 countries, and up through March 2006, [redacted] patients have been exposed to adapalene 0.1% gel, cream, or solution.

Up to March 31st, 2006, the Sponsor reports a total of 163 cases of pregnancies exposed to adapalene (156 patients received adapalene 0.1%, 6 patients received adapalene 0.3%, and 1 patient received several formulations). Of these exposures, there are 97 known pregnancy outcomes. Of these 97, 68 had normal outcome, there were 10 elective abortions, 10 spontaneous abortions, and congenital anomalies in 6 cases.

The sponsor states that the rate of congenital malformations is not statistically different than the background rate, and that the malformations reported in the 6 cases are not consistent with retinoid embryopathy.

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[3] Allec J, Chatelus A, Wagner N. Skin distribution and pharmaceutical aspects of adapalene gel J Am Acad Dermatol. 1997 Jun;36(6 Pt 2):S119-25

[4] Akhaven A, Bershad S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. Am J Clin Dermatol 2003;4(7):473-92.

None of the infants born mothers exposed to 0.3% adapalene had congenital malformations, however, this information is limited.

- **CONCLUSIONS AND RECOMMENDATIONS**

Data for adapalene 0.3% topical gel has been evaluated for the once daily treatment of acne vulgaris in patients 12 years of age and older, and despite initial reservations, the review division has determined that there is a clinical benefit to this formulation when compared to the once daily use of the already marketed adapalene 0.1% topical gel and cream. The increased concentration provides additional clinical benefit and additional risk of systemic exposure.

The original approval of the 0.1% topical formulations included assessment of systemic exposure using an assay with sensitivity lower 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). A direct comparison of the two concentrations was not performed by the Sponsor using the mores sensitive assay, therefore, the data we currently have from submitted studies indicates 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. Literature reports suggest that absorption of the 0.1% formulations is not zero, but it is less than that demonstrated with the 0.3% formulation. It should be noted that the clinical trials are fairly provocative as they approximated 6% BSA involvement, and clinical studies demonstrated that clinical use was less than half of that used in the systemic absorption studies.

A study comparing the systemic exposure of the two formulations using the newer, more sensitive assay may be helpful in helping the division determine relative risk when the adapalene 1% cream and gel is compared with the 0.3% gel, but systemic levels of both formulation strengths are low, and it is difficult to translate those systemic exposure numbers into clinically meaningful recommendations for patients.

There is no new information from animal studies, but there are a few cases of human malformations and spontaneous abortions that occurred when pregnant women were exposed to both the 0.1% and the 0.3% topical formulations. These numbers are not statistically greater than the number that occur in the general population, and the malformations were not consistent with retinoid embryopathy.

Literature reports of three cases of malformations after maternal use of the 0.1% formulation were not compelling. These three cases were all reviewed by DDRE in 2004, and at that time, the recommendation was that current labeling was adequate to address risk.

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).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

DATE: September 8, 2006

FROM: Marilyn R. Pitts, Pharm.D., Safety Evaluator, Team Leader
Office of Surveillance and Epidemiology (OSE)
Division of Drug Risk Evaluation (DDRE)

THROUGH: Mark Avigan, M.D., C.M., Director
Office of Surveillance and Epidemiology (OSE)
Division of Drug Risk Evaluation

TO: Susan Walker, M.D., Director
Division of Dermatologic and Dental Products (DDDP)

SUBJECT: OSE Postmarketing Safety Review (PID D060495)
Sponsor Submission: Worldwide Pharmacovigilance Monitoring of Adapalene Formulations - Monitoring for Pregnancy Data, May 22, 2006
Drug: Adapalene (Differin Gel®, 0.3%, NDA 21-753;
0.1% Gel, NDA 20-380; 0.1% Cream, NDA 20-748)

EXECUTIVE SUMMARY

This document is prepared in response to a request from DDDP to evaluate Galderma's submission of pregnancy exposure information for adapalene topical products.[1]

On June 7, 2006 Galderma submitted the "Worldwide Pharmacovigilance Monitoring of Adapalene Formulations – Monitoring for Pregnancy Data" in which the sponsor reported 163 cases of pregnancy exposures related to using adapalene topical products.[2] Based on a concern that there is a potential for systemic absorption of topical adapalene, the sponsor's submission reviews all adapalene-associated pregnancy exposures (both foreign and domestic) known to Galderma since first marketed in France in 1995 to March 31, 2006. The majority of adapalene's pregnancy exposures occurred post-marketing with the 0.1% formulations, with a small number of exposures occurring with higher concentrations. Fifty-nine percent of the exposures reported a known outcome, including, in order of decreasing frequency, "normal outcome" (58)[3], spontaneous abortion (12), elective abortion (10), and congenital anomaly (6). One case each reported ectopic pregnancy, separation of placenta-fetal death, and premature baby's death.

[1] Galderma Submission on June 7, 2006: Worldwide Pharmacovigilance Monitoring of Adapalene Formulations - Monitoring for Pregnancy Data- May 22, 2006
[2] Adapalene 0.1% is marketed as Differin Cream or Gel and has an assigned Pregnancy Category of C. The product is not contraindicated in pregnancy.
[3] Normal outcome was not defined

Since marketing in 1995 to March 31, 2006, there has been six congenital anomaly cases reported worldwide with adapalene 0.1% formulations. This submission reviewed these six cases, of which five of the congenital anomaly cases were previously known to the FDA, and one case was new. The five previously known cases were included in a 2004 analysis by DDRE.[4] Three of the five were considered potential cases of retinoid-specific, adapalene associated teratogenicity. The sixth new case occurred in a young woman who used topical adapalene 0.1% and topical clindamycin during the first two weeks of her pregnancy. This new case described a variety of congenital anomalies, affecting multiple organ systems, of which two systems (cardiac, brain) are among those commonly affected by retinoid exposure. However, the multiple anomalies that the case described, including Dandy Walker malformation and scimitar syndrome were not consistent with the overall picture of anomalies causally associated with exposure to retinoids.[5]

Marketed adapalene 0.1% products are currently designated pregnancy category C, for which use in pregnancy is not contraindicated. Review of the product labeling shows that adapalene, as well as other topical dermatologic retinoid products are teratogenic in animals. Other topical retinoid products include tazarotene (category X), alitretinoin (category D), and tretinoin (category C). Using any of these products in pregnancy requires balancing the potential risk to the fetus to the potential benefits of using the product, and ranges from being contraindicated in pregnancy (tazarotene), to using in pregnancy if the potential benefit exceed the potential risk (alitretinoin, tretinoin and adapalene).

Spontaneous reporting databases such as AERS are able to detect serious, rare adverse events. However, due to limitations such as under-reporting, and lack of clinical detail in individual cases, AERS is not the optimal tool to detect adverse events that have a latency period of expression. If a congenital anomaly is immediate, catastrophic and easily attributable to a drug product, then AERS maybe able to assist in the detection of a safety signal for the congenital anomaly. However, if the congenital anomaly is subtle, confounded, and have multiple intervening exposures, then AERS may have a more difficult time attributing cause and effect, and therefore identifying a safety signal. Because of these limitations, the value of AERS in identifying a congenital anomaly safety signal is variable. [ ] [ ] [ ] [ ]

[4] Brinker A. Post-Marketing Safety Review: Reports of Pregnancy Exposure/birth defects with topical adapalene; PID # D040185. Office of Drug Safety, Division of Drug Risk Evaluation, May 18, 2004

[5] Lammer EJ, Chen DT, Hoar RM, et al. Retinoic Acid Embryopathy. N Engl J Med. 1985;313(14):837-41

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.

[redacted]

Background

Adapalene 0.1% was approved by the FDA on May 31, 1996, and May 26, 2000, respectively as Differin® gel and cream to topically treat acne vulgaris. Galderma, the sponsor, submitted an application for approval of a higher strength of adapalene (0.3% gel, NDA 21-753), to which the Agency issued a NA letter on February 1, 2005 for the following reasons:

1. The pivotal study failed to demonstrate statistical superiority of the 0.3% gel over the 0.1% gel; and

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 company was asked to address the above deficiencies, and as part of the company's response, Galderma submitted the "Worldwide Pharmacovigilance Monitoring of Adapalene Formulations – Monitoring for Pregnancy Data" on June 7, 2006. DDDP requested DDRE's input on the company's submission, and also requested that DDRE's experience with similar applications be described.

DDRE previously analyzed AERS post-marketing reports of pregnancy exposure with topical adapalene 0.1%. This analysis was conducted by Allen Brinker, M.D., M.S., and is dated May 18, 2004.[6] Dr. Brinker analyzed eight unduplicated reports of adapalene associated pregnancy exposures retrieved from the AERS database. Of the eight cases reviewed, three were potential cases of retinoid-specific, adapalene associated teratogenicity. One of the three cases occurred in France and has been well described in the literature[7]; the two remaining cases included a domestic report provided by a consumer, and a foreign report of an infant with pathology described as "brain damage." From the AERS data alone a compelling safety signal for retinoid-specific birth defects in association with topical adapalene was not identified.

[6] Brinker A. Post-Marketing Safety Review: Reports of Pregnancy Exposure/birth defects with topical adapalene; PID # D040185. Office of Drug Safety, Division of Drug Risk Evaluation, May 18, 2004

This document is organized into two parts:

I. DDRE's Comments on Galderma's submission: Worldwide Pharmacovigilance Monitoring of Adapalene Formulations – Monitoring for Pregnancy Data", and

II. Discussion of other Topical Dermatological Retinoids Pregnancy Labeling

Labeling - Adapalene

Adapalene is indicated to topically treat acne vulgaris, and has retinoid-like pharmacological activity. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors, but unlike tretinoin, adapalene does not bind to the cytosolic receptor protein. Although, the exact mode of action in treating acne vulgaris is unknown, adapalene is a potent modulator of cellular differentiation, keratinization and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Absorption of adapalene through human skin is low. In a pharmacokinetic study with six acne patients treated once daily for five days, there were no quantifiable amounts of Differin® cream in plasma samples from any patient.[8]

Topical adapalene has a pregnancy category C[9] status, and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus:

Part I: Comments on Galderma's submission: Worldwide Pharmacovigilance Monitoring of Adapalene Formulations – Monitoring for Pregnancy Data

The information provided by the sponsor is current to March 31, 2006. At the time of submission, adapalene 0.1% formulations were marketed in as many as 86 countries; however, the 0.3% formulation was not marketed in any country.[11] As of March 31, 2006, Galderma estimated that [ ] patients,

[7] Autret E, Berjot M, Jonville-Bera AP, et al. Anopthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy (letter). Lancet 1997;350(9074):339.
[8] Differin® Cream product labeling, June 2004, extracted from PDR Electronic Library™, August 25, 2006
[9] FDA Pregnancy Category C: Animal reproduction studies have shown an adverse effect, or animal reproduction studies have not been conducted, and the benefits from use of the drug in pregnant women may be acceptable despite its potential risks.
[10] [ ]
[11] The gel was available in 86 countries; the cream in 61 countries; and the solution was available in 26 countries.

of which women comprised approximately 64%, had been exposed to adapalene 0.1% topical formulations.

The sponsor did not submit actual MedWatch forms of the reported pregnancy exposures for review with the submission, but a table of abstracted data. The following information is obtained from the sponsor's submission, and does not represent original analysis by DDRE.

Worldwide, there were 163 cases of pregnancy exposure to adapalene formulations, including 156 exposures to adapalene 0.1%; six exposures to adapalene 0.3%; and one exposure to multiple concentrations (0.5%, 0.2% and 0.3%) which occurred during a clinical trail. The exposures are categorized as follows:

A. Post-marketing Pregnancy Exposure Reports (n = 126)

- 64 of 126 pregnancy exposures had known outcomes; these outcomes included "normal outcome" (49), elective abortion (3), spontaneous abortion (6), structural malformations (5) and functional anomaly (1). The cases of structural malformation and functional anomaly are discussed later in the document.
- 51 of 126 reports were lost to follow-up
- 11 of 126 reports were "on-going"
- All 126 of the post-marketing exposure cases were reported with adapalene 0.1% formulations
- All six cases reporting congenital anomalies reported using adapalene 0.1%

B. Clinical Trial Pregnancy Exposure Reports (n = 37)

- 33 of 37 clinical trial pregnancy exposure reports had known outcomes; these known outcomes included "normal outcome" (19), elective abortion (7), spontaneous abortion (6), ectopic pregnancy (1), separation of placenta – fetal death (1) and premature baby's death (1).
- 4 of 37 clinical trial pregnancy exposure reports were lost to follow-up
- 30 of the 37 clinical trial pregnancy exposures were reported with 0.1% adapalene; six of the exposures were to adapalene 0.3%, and one exposure was to multiple strengths (0.05%, 0.2% and 0.3%)
- Six of the 0.3% pregnancy exposures, and the one exposure with the multiple strengths had known outcomes. These known outcomes included "normal" (4) and elective abortion (2). One 0.3% exposure case was lost to follow-up.
- There were no congenital anomalies reported during clinical trials, or with the 0.3% formulation

Congenital Anomalies

A chart of the six congenital anomalies cases obtained from the sponsor's submission is in the appendix. Since the sponsor did not submit MedWatch forms for analysis, we were only able to abstract the information from the sponsor's narrative information. According to the sponsor's narrative information there were no congenital anomalies reported with the 0.3% formulation or during clinical trials. All six congenital anomalies were reported with the 0.1% formulations, and all occurred post-marketing. Five of the six cases were previously included in Dr. Brinker's 2004 analysis and do not represent new cases.[12] There is only one new case of a congenital anomaly in the sponsor's submission. The new case describes congenital anomalies that occurred after the fetus was exposed to topical adapalene 0.1% and topical clindamycin during the first two weeks of pregnancy. This new case described multiple congenital anomalies that do not appear to be related to retinoid exposure. Although the case reported some organ system anomalies similar to retinoid exposure (e.g. cardiac and brain defects), the majority of the anomalies were not consistent with retinoid exposure.[13]

Part II: Pregnancy Labeling Status and Risk Minimization Considerations for other Topical Dermatological Retinoids

Other topical retinoids used in dermatology include tazarotene, alitretinoin, and tretinoin. These topical retinoids carry pregnancy labeling categories of X (tazarotene), D (alitretinoin), and C (tretinoin). We could not find an algorithm that described how the various pregnancy categories were assigned to these topical retinoids; however, we expect that various characteristics of the drug products, as well as the conditions being treated would weigh into the pregnancy category assignments. Factors that may have influenced the pregnancy category assignments include:

- The potential or actual demonstration of systemic absorption of these teratogenic products;
- The surface area of application; applying products to acne, which is primarily limited to the face is expected to result in less of an opportunity of absorption compared to applying products to treat psoriasis (which has the potential of affecting large body surface areas);
- The balance of potential risk of using these teratogenic products to the potential benefit of treatment.

[12] Case #s: FI20000001, FR19960020, FR199636045.2, FR19970008.2, USGD0310554

[13] Combination of craniofacial, cardiac, thymic and central nervous system defects; including microtia/anotia, micrognathia, cleft palate, conotruncal heart defects and aortic-arch abnormalities, thymic defects, retinal or oprtic-nerve abnomalities and central nervous system malformations.

Additional pregnancy information is also in the Contraindications and Warnings sections of the labeling for topical tazarotene, in the Warnings section for alitretinoin, and in the Precautions section for tretinoin products. There are no additional risk minimization tools[14] employed for the topical retinoid products.

Topical Tazarotene (Tazorac®, Pregnancy Category X)[15]

Tazarotene is a retinoid prodrug that is converted to its active form tazarotenic acid. Tazarotenic acid binds to all three members of the retinoic acid receptor family.[16] Topical tazarotene is indicated to treat psoriasis and acne, and is a teratogenic substance that produces fetal abnormalities in animals that are exposed in utero. The abnormalities are consistent with retinoid exposure.[17]

Following topical application, tazarotene is hydrolyzed to its active form tazarotenic acid and is systemically absorbed. Systemic absorption was determined to be less than 1% of the applied dose (without occlusion) in six psoriatic patients, and approximately 5% of the applied dose (under occlusion) in six healthy subjects. Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals. There may be less systemic absorption when treating acne of the face alone due to less surface area for application. However, tazarotene is a teratogenic substance, and it is unknown what level of exposure is required for teratogenicity in humans.

Topical tazarotene's label reports that [ ] [ ] topical tazarotene is designated pregnancy category X, and its use during pregnancy is contraindicated. The Warnings section of the label states that women of child bearing potential should use adequate birth-control measures while using topical tazarotene; and that a negative pregnancy test should be obtained within 2 weeks of starting topical tazarotene; and that topical tazarotene should be started during a normal menstrual period. [18]

Topical Alitretin (Panretin®, Pregnancy Category D)[19]

Alitretinoin (9-*cis*-retinoic acid) is a naturally occurring endogenous retinoid that binds and activates all know intracellular retinoid receptor subtypes.[20] Alitretinoin inhibits the growth of Kaposi's sarcoma

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[14] Risk Minimization Tools include Education and Outreach, "Guiding" Systems and Performance Linked Access Systems

[15] FDA Pregnancy Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

[16] RARα, RARβ, RARγ, but shows relative selectivity for RARβ and RARγ,

[17] Single incidences of retinoid malformations, including spina bifida, hydrocephaly, heart anomalies

[18] Tazaroc® Product Label, Allergan, December 2003

[19] FDA Pregnancy Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

cells in vitro, and is indicated to topically treat cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.[21] 9-*cis*-retinoic acid has been shown to be teratogenic in animals.

According to the label, although there are no detectable plasma concentrations of 9-*cis*-retinoic acid metabolites after topical application of alitretinoin, in vitro studies indicate that the drug is metabolized to two metabolites, one of which is the major circulating metabolite found following oral administration of 9-*cis*-retinoic acid. Although animal reproduction studies with topical 9-*cis*-retinoic acid have not been conducted, oral 9-*cis*-retinoic acid has been shown to be teratogenic in animals. It is not known whether topical Panretin® gel can modulate endogenous 9-*cis*-retinoic acid levels in a pregnant woman, nor whether systemic exposure is increased by application to ulcerated lesions or by duration of treatment.

Topical alitretinoin is designated pregnancy category D, and its use in pregnancy is not contraindicated. The Precautions section of the label warns that Panretin® gel could cause fetal harm if significant absorption were to occur in a pregnant woman; women of child-bearing potential should be advised to avoid becoming pregnant.[22]

Topical Tretinoin (Retin-A®, Retin-A Micro®, Avita®, Renova®, Altinac®; Pregnancy Category C)[23]

Topical tretinoin is all-trans-retinoic acid and is available as a cream, gel and solution to topically treat acne vulgaris. Although, oral tretinoin has been shown to be teratogenic in animals (rats, mice, hamsters and subhuman primates), topical tretinoin teratogenicity tests have generated equivocal results. Several well-controlled animal studies have shown that dermally applied tretinoin may be fetotoxic, but not overly teratogenic in rats and rabbits. There are no adequate and well-controlled studies in pregnant women. Topical tretinoin is designated pregnancy category C, and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

According to the 2002 Retin-A label, 30 human cases of temporally associated congenital malformations have been reported during two decades of clinical use. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth

[20] RARα, RARβ, RARγ, RXRα, RXRβ and RXRγ
[21] Panretin® Product Label, Ligand Pharmaceuticals Incorporated, October, 2001; http://www.ligand.com/pdf/PANRETINGELPI.PDF
[22] Panretin® Product Label, Ligand Pharmaceuticals Incorporated, October, 2001; http://www.ligand.com/pdf/PANRETINGELPI.PDF
[23] FDA Pregnancy Category C: Animal reproduction studies have shown an adverse effect, or animal reproduction studies have not been conducted, and the benefits from use of the drug in pregnant women may be acceptable despite its potential risks.

defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.[24]

DISCUSSION/CONCLUSION

The sponsor reported 163 cases of pregnancy exposure related to topical adapalene products. The majority of the exposures occurred post-marketing with the 0.1% formulations, with a small number of exposures occurring with higher concentrations. Fifty-nine percent of the exposures reported a known outcome, including, in order of decreasing frequency, "normal outcome" (58)[25], spontaneous abortion (12), elective abortion (10), and congenital anomaly (6). One case each reported ectopic pregnancy, separation of placenta-fetal death, and premature baby's death.

The six congenital anomaly cases reported with topical adapalene were reported with the 0.1% formulation. Five cases were previously known to the FDA, and one case was new. The five previously known cases were included in a 2004 analysis by DDRE where three of the five were considered potential cases of retinoid-specific, adapalene associated teratogenicity. However, at the time of review, the three cases did not appear to represent a compelling safety signal for retinoid-specific birth defects associated with adapalene use. The sixth case was new to the Agency and described a variety of congenital anomalies (affecting multiple organ systems) which were not consistent with the overall picture of anomalies associated with exposure to retinoids.

Marketed adapalene 0.1% products are currently designated pregnancy category C, and use in pregnancy is not contraindicated. Topical adapalene can be used in pregnancy if the potential benefits exceed the potential risk of the product. Review of the product labeling shows that adapalene, as well as other topical dermatologic retinoid products are teratogenic in animals. Other topical retinoid products include tazarotene (category X), alitretinoin (category D), and tretinoin (category C). Using any of these products in pregnancy requires balancing the potential teratogenic risk to the fetus to the potential benefits of using the product, and ranges from being contraindicated in pregnancy (tazarotene), to using in pregnancy if the potential benefit exceed the potential risk (alitretinoin, tretinoin and adapalene). Additionally, the tazarotene labeling (possibly due to category X status) offers the strongest language of the four in recommending adequate contraception during treatment, and ensuring a negative pregnancy status prior to

[24] Retin-A Product Label,
[25] Normal outcome was not defined

starting treatment. Only two of the four labels (tazarotene and tretinoin) describe human pregnancy outcome information.

Spontaneous reporting databases such as AERS are able to detect serious, rare adverse events. However, due to limitations such as under-reporting, and lack of clinical detail in individual cases, AERS is not the optimal tool to detect adverse events that have a latency period of expression. If a congenital anomaly is immediate, catastrophic and easily attributable to a drug product, then AERS maybe able to assist in the detection of a safety signal for the congenital anomaly. However, if the congenital anomaly is subtle, confounded, and have intervening exposures, then AERS may have a more difficult time attributing cause and effect, and therefore identifying the safety signal. Because of these limitations, the value of AERS in identifying a congenital anomaly safety signal may be difficult. [redacted]

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.

[redacted]

(signed September 8, 2007)

Marilyn R. Pitts, Pharm.D., Safety Evaluator, Team Leader Date

cc:
NDA 21-753, 20-380, 20748
DDDP Walker/Luke/Cook/Kozma-Fornaro/Wright/Division File
DDRE Avigan/Johann-Liang/Wahab/Pitts/Robinson/Brinker/Division File

Appendix: Congenital Anomaly Cases Reported by Galderma's May 22, 2006 Submission

Case #	Location	Congenital Anomaly	Product	When Exposed	Comments
FI20000001	Foreign	Functional anomaly Trampling of feet, swallowing absent, absent primitive reflex; clinical signs of serious brain damage	Adapalene 0.1%	1st trimester Between weeks 6 and 10 of mother's pregnancy	Case previously described by Brinker, 2004
FR19960020	Foreign	Structural malformation Extreme anophtalmia or microphtamia?, absence of callus corpus without another malformation, agenesia of the optical chiasma and of the eyeball	Adapalene 0.1%	1st trimester One month before pregnancy, and continued through week 13 of pregnancy	Case previously described by Brinker, 2004
FR199636045.2	Foreign	Structural malformation Living male at 9 months delivered with single kidney and single umbilical artery	Adapalene 0.1%	3rd trimester Applied twice during 9th month of pregnancy	Case previously described by Brinker, 2004.
FR19970008.2	Foreign	Structural malformation Live male delivered with hypotonia, facial dysmorphy. Aarskog's syndrome suspected (monogenic x-linked recessive disorder) because two oldest sons were born with same syndrome	Adapalene 0.1%	1st trimester Twice daily during 1st 3 months of pregnancy	Case previously described by Brinker, 2004.
USGD0310554	US	Structural malformation Cleft lip, cleft palate, brain,gastric, cardiovascular, intestinal anomalies	Adapalene 0.1% gel	1st, 2nd trimester exposure	Case previously described by Brinker, 2004.
CHGDP0511971	Foreign	Structural malformation Scimitar syndrome which included partial abnormal pulmonary vein drainage, right lung hypoplasia, cardiac arrhythmia, right lower lung sequestration; atrial septum defect, dysplasia of aortic valve, hypospadias glans penis, right inguinal hernia, Dandy walker malformation. Normal caryotype	Adalapene 0.1% gel + topical clindamycin	1st trimester Applied agents during first two weeks of pregnancy	New Case. Some cardiac and brain anomalies; however, total anomalies are inconsistent with retinoid exposure

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/s/

Marilyn Pitts
9/11/2006 12:52:16 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
9/11/2006 01:01:58 PM
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ADDENDUM to MEMORANDUM

Date: October 11, 2006

From: Lisa L. Mathis, M.D.

To: David Kettl, MD
Millie Wright
DDDP, ODE 3
Office of New Drugs

Subject: Differin (adapalene) gel, 0.3%

Date of Original Memorandum: July 27, 2006

Reason for Addendum: This addendum is being submitted to correct an error in the original memorandum on page 5, fifth paragraph in italics under "Review of Data." This error named the primary pharm/tox reviewer twice instead of stating that there were two different reviewers with the differing opinions. In order to clarify attribution of recommendations, the new paragraph reads:

The primary pharm/tox reviewer (Dr. Mainigi) recommended approval of the 0.3% formulation with no change in the pregnancy category C as was the category for the 0.1% approved formulation. The pharm/tox team leader Dr. Brown) recommended [redacted]

The complete and corrected memorandum is contained below:

Consult Question: Differin (adapalene) 0.1% is indicated for the treatment of acne vulgaris and is a pregnancy category C. A NDA has been submitted for a 0.3% gel, and the Sponsor has been requested to initiate 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. There is a question regarding need to change pregnancy category based on higher systemic exposure of the 0.3% topical gel when compared to the 0.1% topical formulations.

- **EXECUTIVE SUMMARY**

Differin (adapelene), 0.1% 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) and gel (NDA 20-380) since 5/31/1996, and as a 0.1% cream (NDA20-748) since 5/26/2000. The 0.1% solution has been discontinued. A New drug Application (NDA) was submitted 1 April 2004 for adapelene gel, 0.3%, and while it has been established that there is clinical benefit of the increased concentration gel, there is still question regarding safety. The current labeling for the 0.1% topical formulations includes a pregnancy category C, but with the potential for increased systemic exposure from the use of the 0.3% gel, the Division of Dermatologic and Dental Products has question regarding the safety of this product in women who may become pregnant.

Adapalene is a synthetic analog of retinoic acid selectively binds to RARβ and –γ nuclear receptors of retinoic acid. Retinoids are known teratogens when there is significant systemic exposure. Retinoic Acid embryopathy consists of craniofacial, cardiovascular, and central nervous system defects as well as thymic and parathyroid abnormalities.

The original approval of the 0.1% topical formulations included assessment of systemic exposure using an assay with sensitivity lower 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). A direct comparison of the two concentrations was not performed by the Sponsor using the mores sensitive assay, therefore, the data we currently have from submitted studies indicates 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. Literature reports suggest that absorption of the 0.1% formulations is not zero, but it is less than that demonstrated with the 0.3% formulation. It should be noted that the clinical trials are fairly provocative as they approximated 6% BSA involvement, and clinical studies demonstrated that clinical use was less than half of that used in the systemic absorption studies.

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.

Consideration should be given to including information about reported cases of pregnancy exposures in the ADVERSE EVENTS section of labeling, if this information can be brief.

- **BACKGROUND**

Differin (adapelene), 0.1% 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) and gel (NDA 20-380) since 5/31/1996, and as a 0.1% cream (NDA20-748) since 5/26/2000. The 0.1% solution has been discontinued.

Adapalene is a synthetic analog of retinoic acid selectively binds to RARβ and –γ nuclear receptors of retinoic acid. Retinoids are known teratogens when there is significant systemic exposure. Retinoic Acid embryopathy consists of:

- Craniofacial defects that may include: facial asymmetry, microtia and/or anotia with stenosis of the external ear canal, posterior helical pits, facial nerve palsy ipsilateral to malformed ear, narrow sloping forehead, micrognathia, flat depressed nasal bridge, ocular hypertelorism, and mottling of teeth
- Cardiovascular defects that may include: conotruncal malformations, including transposition of the great vessels, tetralogy of Fallot, truncus arteriosus communis, supracristal ventricular septal defect, aortic arch interruption, retroesophageal subclavian artery, aortic arch hypoplasia, and hypoplastic left ventricle, and
- Central nervous system defects that may include: hydrocephalus, microcephaly, structural errors of cortical and cerebellar neuronal migration and gross malformations of posterior fossa structures),
- Subnormal range of intelligence, and
- Sometimes thymic and parathyroid abnormalities.

Current Labeling:
The CLINICAL PHARMACOLOGY section of labeling states the following:
"Pharmacokinetics: Absorption of adapalene from DIFFERIN® Cream through human skin is low. In a pharmacokinetic study with six acne patients treated once daily for 5 days with 2 grams of DIFFERIN® Cream applied to 1000 cm^2 of acne involved skin, there were no quantifiable amounts (limit of quantification = 0.35 ng/mL) of adapalene in the plasma samples from any patient. Excretion appears to be primarily by the biliary route."

The PRECAUTIONS section of labeling for the 0.1% adapelene topical formulations states the following:
"Pregnancy: **Teratogenic effects. Pregnancy Category C.** No teratogenic effects were seen in rats at oral doses of 0.15 to 5.0 mg/kg/day adapalene (up to 20 times the MRHD based on mg/m^2 comparisons). However, adapalene administered orally at doses of 25 mg/kg, (100 times the MRHD for rats or 200 times MRHD for rabbits) has been shown to be teratogenic. Cutaneous teratology studies in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day (24 times the MRHD for rats or 48 times the MRHD for rabbits) exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-

controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Additional Safety information:
A safety review was conducted May 19, 2004 by Division of Drug Risk Evaluation. A review of the AERS database and medical literature recovered three potential cases of retinoid specific, adapalene gel-associated teratogenicity (US 7/2003, Finland 1/2001, France 10/1996). One of these cases occurred in France and has been well described in the medical literature.[1,2] The other two cases include a domestic report provided by a consumer and an infant with pathology described only as "brain damage" from Finland. Postmarketing adverse event data did not suggest a compelling safety signal for retinoid-specific birth defects in association with topical adapalene and no changes to labeling were recommended.

Differin (adapelene) gel, 0.3%
A New drug Application (NDA) was submitted 1 April 2004 for adapelene gel, 0.3%. The action taken on this application 1 February 2005 was a nonapproval (NA) with the following deficiencies noted:

1. "The pivotal study failed to demonstrate statistical superiority of the 0.3% adapalene gel over Differin (adapelene) Gel, 0.1%. Therefore, there is insufficient information to support the increased risk of the higher concentration.
2. The higher concentration of adapelene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%."

The sponsor 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."

A guidance meeting was held 12 October 2005 to provide guidance on the two deficiencies listed in the NA letter. Concurrence was reached on point #1, that the 0.3 % formulation wins over the 0.1 % gel despite reservations about the robustness of the data from the Biostatics team. It was noted in the 10/12/05 minutes 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 dependant on a demonstration that the benefit outweighs the risk which may not be evident for Differin 0.3%."

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[1] Autret E, Berjot M, Jonville-Bera AP, et al. Anopthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy (letter). Lancet 1997;350(9074):339
[2] Birth defects due to topical adapalene and tretinoin. Prescrire Int 1998;7(37):148-9

The Clinical Pharmacology reviewer noted that "The Sponsor could conduct a study to compare the systemic exposure of 0.1% and 0.3% gel 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). The results from this study would 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." This recommendation was based on the fact that the initial approval of the adapelene 1% formulations was based on data using an analytical method with a LOQ of $\leq$0.35 ng/mL where no systemic exposure was noted. Also, the reviewers were concerned that the studies only enrolled patients who has approximately 5-6% BSA involvement when the estimated maximal BSA involvement may be >6% BSA. It should be noted that when one is using %BSA, a difference of 1% may not be clinically relevant, especially given that in clinical trials, patients only used about 1 gram per day – meaning that the clinical %BSA involvement was closer to 3% BSA.

- **REVIEW OF DATA**

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 no change in the pregnancy category C as was the category for the 0.1% approved formulation. The pharm/tox team leader Dr. Brown) recommended [redacted]

Clinical Pharmacology: Increase in systemic exposure from 0.3% gel would result in greater systemic risk. 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 perfrmed 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.

*It should be noted that the Sponsor evaluated systemic exposure of adapalene in patients following application of 2 g of adapalene 0.3%, gel per day to the diseased skin that covered a skin area of about 1000 cm^2 (~5-6% BSA) for 10 days. Although this dose did not represent that of patients with large BSA involvement (>6% BSA), the 2 g/day dose is clinically relevant 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. In actual use, the 2 grams would overestimate the actual usage condition exposure.

Literature reports:

There are a few literature reports of systemic exposure with adapalene 0.1% topical gel.[3] A liberation/penetration study demonstrated that significant quantities of adapalene were present in epidermis and dermis, but only 0.01% of the applied dose penetrated through the skin. [4]

[3] Allec J, Chatelus A, Wagner N. Skin distribution and pharmaceutical aspects of adapalene gel J Am Acad Dermatol. 1997 Jun;36(6 Pt 2):S119-25

[4] Akhaven A, Bershad S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. Am J Clin Dermatol 2003;4(7):473-92.

Clinical Experience: Adapalene topical formulations, 0.1%, have been marketed worldwide since 1995. These products are approved for the treatment of acne vulgaris in 86 countries, and up through March 2006, [ ] patients have been exposed to adapalene 0.1% gel, cream, or solution.

Up to March 31st, 2006, the Sponsor reports a total of 163 cases of pregnancies exposed to adapalene (156 patients received adapalene 0.1%, 6 patients received adapalene 0.3%, and 1 patient received several formulations). Of these exposures, there are 97 known pregnancy outcomes. Of these 97, 68 had normal outcome, there were 10 elective abortions, 10 spontaneous abortions, and congenital anomalies in 6 cases.

The sponsor states that the rate of congenital malformations is not statistically different than the background rate, and that the malformations reported in the 6 cases are not consistent with retinoid embryopathy.

None of the infants born mothers exposed to 0.3% adapalene had congenital malformations, however, this information is limited.

- **CONCLUSIONS AND RECOMMENDATIONS**

Data for adapalene 0.3% topical gel has been evaluated for the once daily treatment of acne vulgaris in patients 12 years of age and older, and despite initial reservations, the review division has determined that there is a clinical benefit to this formulation when compared to the once daily use of the already marketed adapalene 0.1% topical gel and cream. The increased concentration provides additional clinical benefit and additional risk of systemic exposure.

The original approval of the 0.1% topical formulations included assessment of systemic exposure using an assay with sensitivity lower 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). A direct comparison of the two concentrations was not performed by the Sponsor using the mores sensitive assay, therefore, the data we currently have from submitted studies indicates 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. Literature reports suggest that absorption of the 0.1% formulations is not zero, but it is less than that demonstrated with the 0.3% formulation. It should be noted that the clinical trials are fairly provocative as they approximated 6% BSA involvement, and clinical studies demonstrated that clinical use was less than half of that used in the systemic absorption studies.

A study comparing the systemic exposure of the two formulations using the newer, more sensitive assay may be helpful in helping the division determine relative risk when the adapalene 1% cream and gel is compared with the 0.3% gel, but systemic levels of both formulation strengths are low, and it is difficult to translate those systemic exposure numbers into clinically meaningful recommendations for patients.

There is no new information from animal studies, but there are a few cases of human malformations and spontaneous abortions that occurred when pregnant women were exposed to both the 0.1% and the 0.3% topical formulations. These numbers are not statistically greater than the number that occur in the general population, and the malformations were not consistent with retinoid embryopathy.

Literature reports of three cases of malformations after maternal use of the 0.1% formulation were not compelling. These three cases were all reviewed by DDRE in 2004, and at that time, the recommendation was that current labeling was adequate to address risk.

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).

Addendum added by Dr. Kweder 7/27/06
"Recommend label include information about reports of pregnancy exposures if it can be brief."