CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-502

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA Number: **22-502**

SERIAL NUMBER: NOOO

DATE RECEIVED BY CENTER: **03/02/09**

PRODUCT: **DIFFERIN™ (adapalene) Lotion 0.1%**

INTENDED CLINICAL POPULATION: Subjects above 12 years of age

SPONSOR:	Galderma Laboratories, L.P.
	14501 N. Freeway, FortWorth, TX 76177
REVIEW DIVISION:	Division of Dermatology and Dental Products (HFD-540)
PHARM/TOX REVIEWER:	Kumar D. Mainigi
PHARM/TOX SUPERVISOR:	Barbara Hill
DIVISION DIRECTOR:	Susan Walker
PROJECT MANAGER:	Kelisha Turner

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approvable

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: The draft submitted by the sponsor is acceptable with little modification.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Irrespective of the nature of the formulation and or the drug concentration, the average topical absorption of adapalene in most species including humans did not exceed 5 percent. In most species, no significant drug accumulation was observed in the dermal studies of any duration. The low drug accumulation on repeated applications indicated fast metabolism. Adapalene is extensively biodegraded in animals and humans, and the parent drug and metabolites are mainly found in organs (liver, GI-tract) involved in the excretory metabolism. However, metabolic pathways and metabolites of adapalene are not completely characterized.

In the 3-month minipig dermal study conducted with Differin Lotion 0.1% (0.0, 0.2, 0.6, and 1.2mg adapalene/kg/day), absolutely no systemic toxicity was observed at the highest dose level. On day 1, the plasma drug level was below the detection limit in all the drug treated groups. However, the repeated topical applications resulted in some drug accumulation which did not translate into any systemic toxicity. The minimal skin irritation developed at all dose levels was much reduced during the one-month recovery period. The NOAEL for systemic and local toxicity was established at 1.2mg/kg.

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

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

Adapalene has been evaluated as safe at much higher dose levels, thus the topical applications of 36mg adapalene/m^2/day (0.3% gel) for 4-26 weeks did not cause any systemic toxicity in rats. The dose-related scab formation and acanthosis disappeared during 8 weeks of recovery period. Dogs treated topically at the same dose level for

26 weeks did not exhibit any bone-related toxicity; and the epidermal hyperplasia and superficial inflammation developed on the application sites were mild and transient in nature.

In the oral studies (1-500mg adapalene/kg/day), loss of hairs, body weight, spontaneous long bone fractures, and skeletal resorption resembled hypervitaminosis A syndrome.

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

In the mouse dermal carcinogenicity study, no drug-related neoplastic lesions were observed. In the rat oral carcinogenicity study, the high-dose males (1.5mg/kg/day) exhibited a significant ($p<0.05$) incidence of benign pheochromocytoma of the adrenals. The combined number of benign and malignant pheochromocytoma, and pancreatic islet cell tumors in drug-treated males indicated a higher incidence. Accordingly, the high incidence of pheochromocytoma is a characterisitic of compounds acting like retinoids. Moreover, there are many morphological and biochemical differences between the adrenal glands of the rat and man. In addition, the incidence of pheochromocytoma in man is very low (0.005 to 0.09%). A high incidence of carcinomas and adenomas of thyroid was also observed in the drug treated females.

No photocarcinogenicity study was conducted.

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

In the dermal teratology studies (6mg adapalene/kg/day) in rats and rabbits, no teratologic changes were observed. However, in the oral rat and rabbit studies (5, 25, and 60mg adapalene/kg/day), significant teratologic changes (skeletal and visceral malformations) were recorded at 25mg/kg/day and higher dose levels.

In rats, the placenta acted as a partial barrier to drug and its metabolites during organogenesis and thereafter. Adapalene is also secreted in the milk of rats.

In the prenatal and postnatal development studies (0.15, 1.5, and 15mg adapalene/kg/day), the highest dose of adapalene had no effect on the evaluated litter parameters (development after weaning, mating and fertility) of F_0 and F_1 generations, and on F_2 fetuses. Since adapalene was excreted in the milk, it is inferred that the pups were exposed both *in utero* and during lactation.

B. Pharmacologic activity

Adapalene in addition to displaying typical retinoid effects (e.g. normalization of the maturation of follicular epithelium) also exhibits some anti-inflammatory properties. However, some pharmacodynamic differences separate adapalene from tretinoin. First, although adapalene binds to specific retinoic acid nuclear receptors (RARα, RARß, and RARγ), the affinity of adapalene for RARα is much lower than tretinoin. 9-*cis*-retinoic acid has been established as a physiologic ligand of tretinoin, not adapalene. Second, unlike tretinoin, adapalene does not bind to cellular retinoid binding protein II (CRAB II). Possibly, due to these differences, the dermal lesions caused by retinoid like biological activity of adapalene are always much less severe and transient in nature.

Animal studies have indicated that adapalene is a potent modulator of cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris. Thus, topical adapalene normalized the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. It also inhibited the lipoxidation of arachidonic acid to inflammatory mediators.

In conclusion, from the non-clinical safety view point, DIIFERIN (adapalene) Lotion 0.1% was well tolerated.

C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

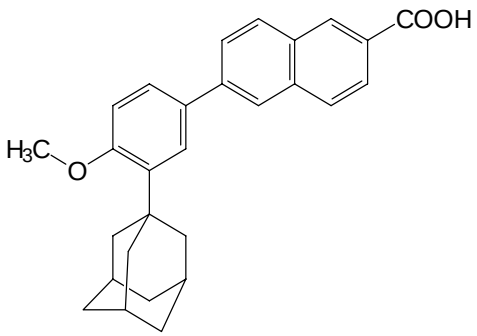
Adapalene formulations for the treatment of *acne vulgaris* are sold in several European, African, Latin and North American countries and Australia. Two products, DIFFERIN™ (adapalene solution) Solution 0.1% (NDA 20-338) and DIFFERIN™ (adapalene gel) Gel 0.1% (NDA 20-380) have been marketed in the United States since August 1996. DIFFERIN™ (adapalene) Cream 0.1% (NDA 20-748) and DIFFERIN® XP™ Gel (adapalene 0.3%) (NDA 21-753) were approved in May 2000 and June 2007, respectively. Now, for the same indication, the sponsor is requesting approval for 0.1% lotion formulation under the 505(b)(1) regulatory route.

NDA number: **022-502**
Review number: 001
Sequence number/date/type of submission: N1/03-02-2009/original
Information to sponsor: No
Sponsor and/or agent: Galderma Laboratories, L.P.
14501 N. Freeway, Fort Worth, TX 76177
Manufacturer for drug substance: Laboratories Galderma SA
Alby-Sur-Chem-Cheran, France

Reviewer name: Kumar D. Mainigi
Division name: Dermatology and Dental Products (**HFD #: 540)**

Drug:

Trade name: Adapalene (Differin) Lotion, 0.1%
Generic name: None
Code names: CD271, AL02866, and SL65.0339
Chemical names:
1) 2-Naphthalenecarboxylic acid, 6-(4-methoxy-3- tricyclo[3.3.1.1^{3,7}]dec-1-ylphenyl-;
2) 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid
CAS registry number: 106685-40-9
Molecular formula/molecular weight: $C_{28}H_{28}O_3$/412.52
Structure:



Relevant INDs/NDAs/DMFs:

INDs. (b) (4)

33, 540 (Gel), Dermatological Products of Texas, Inc., Fort Worth, TX
38, 508 (Cream), Owen/Galderma Laboratories, Inc., Fort Worth
67, 801 (Gel), Galderma Laboratories, Fort Worth, TX

NDAs 20-338 DIFFERIN^{R} (adapalene solution) Solution 1% approved, 05/31/1996
20-380 DIFFERIN^{R} (adapalene gel) Gel 0.1%, 05/31/1996
20-748 DIFFERIN^{R} (adapalene) Cream 0.1%, 05/26/2000
21-753 DIFFERIN^{R} XPTM (adapalene gel, 0.3%), 06/19/2007
22-320 EPIDUO^{TM} (adapalene 0.1%+BZPO 2.5%) Gel

Drug class: Naphthenic acid class of anti-acne agent
Indication: Treatment of *acne vulgarism*
Intended clinical population: Subjects above 12 years of age

Clinical formulation:

Ingredient	**Function**	**Mg/g**
Adapalene	Active agent	1.0
Disodium edentate, USP	(b) (4)	
Propylparaben, NF		
Carbomer 9(b)1, NF		
Methylparaben, NF		
Poloxamer 124, NF		
Phenoxyethanol, NF		
Stearyl alcohol, NF		
PPG-12/SMDI copolymer		
Propylene glycol, USP		
Polyoxy-6 & Polyoxyl-32 palmitostearate		
Medium chain triglycerides		
Sodium hydroxide, NF		
Purified water, USP		
Total		100.0

Route of administration: Topical
Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

1. Four-week dose range-finding study in minipigs
2. Three-month dermal study in minipigs with one-month recovery

Studies not reviewed within this submission: The following studies were reviewed under IND 76, 057.

1. Primary dermal irritation in rabbits
2. Delayed contact hypersensitivity in guinea pigs

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: No studies were conducted with the lotion formulation.

Adapalene a synthetic napthoic acid derivative exhibits biological activities similar to retinoids. However, there are some basic differences between adapalene and retinoids like tretinoin. Although, adapalene also binds to specific retinoic acid nuclear receptors, but unlike tretinoin it does not bind to cellular retinoid binding protein II (CRAB II). Second, whereas in gene transactivation assays with subtypes of human retinoic receptors (RARα, RARß, and RARγ), tretinoin exhibited equally strong transcriptional activation of all three RAR receptors, the activity of adapalene for RARα was much lower than tretinoin. Next, 9-*cis*-retinoic acid is a physiologic ligand of tretinoin, not adapalene.

In addition to displaying typical retinoid like effects (e.g. normalization of the maturation of follicular epithelium), adapalene also exhibits anti-inflammatory properties. In addition, like retinoic acid, adapalene also inhibits transglutaminase I, an enzyme involved in the terminal differentiation of keratinocytes. The drug also exhibits comedolytic activity in Rhino mouse containing a high density of spontaneous "comedones".

2.6.2.2 Primary pharmacodynamics: The multifactorial processes leading to acne vulgaris include disruption of normal process of epidermal maturation (keratinization), excessive secretion from the sebaceous glands of the skin, and an inflammatory immune response. Keratinization involves growing and shedding of cells that lines the pores and glands of the skin. Disruption of this process in acne vulgaris leads to overproduction (hyperkeratosis) of epithelial cells in the follicular infundibulum of the sebaceous gland. Acne vulgaris is comprised of two types of primary lesions: 1) non-inflammatory lesions called open (blackheads) and closed (whiteheads) comedones; and 2) inflammatory lesions (papules, pustules, and nodules) resulting from excessive growth of *Propionibacterium acnes* which interacts with sebum to generate inflammatory agents. In addition to primary lesions, scars due to complication of inflammation are also formed.

The pharmacodynamic studies conducted by the sponsor have indicated that topical adapalene normalized the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. In cultured human keratinocytes, adapalene inhibited the activity of transglutaminase I, a membrane bound enzyme involved in terminal differentiation of keratinocytes (i.e. formation of stratum corneum). The data of both *in vivo* and *in vitro* studies had revealed that the drug also blocked the chemotactic (directional) and chemokinetic (random) responses of human polymorphonuclear leukocytes. It also inhibited the oxidation of arachidonic acid to inflammatory mediators.

2.6.2.3 Secondary pharmacodynamics: Like tretinoin**,** 0.1% adapalene gel was efficient in repairing the signs of UVB-induced photodamage (acanthosis, inflammation, elastosis etc.) on the skin of hairless mice. Both compounds induced a significant increase in the number and size of "repair zones".

2.6.2.4 Safety pharmacology: In the 90-day minipig study (0.0, 0.2, 0.6, and 1.2mg adapalene/kg/day) with 0.1% lotion, no changes in electrocardiograms and blood pressure were observed during the treatment and one-month recovery periods. The safety pharmacology studies with adapalene had also been conducted at much higher dose levels. Thus, the gavage doses (10, 30, 100mg/kg) of adapalene did not affect the behavior, physical health, spontaneous locomotor activity, hexobarbital sleeping time, pain response, basal tone of ileum, and gastrointestinal motility in CD-1 mice. However, in 2-5 post-dose hours at the mid- and high dose levels, drug caused a moderate transient decrease in body temperature. The oral doses at the same levels did not affect the functioning of the cardiovascular, respiratory, and central nervous systems in beagle dogs, and urine volume and electrolyte excretion in Wistar rats.

Abuse liability: Not known

2.6.2.5 Pharmacodynamic drug interactions: No studies were conducted

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: In the 3-month minipig dermal study (0.0, 0.2, 0.6, and 1.2mg/kg/day) with 0.1% lotion, no drug was detected in the plasma on day 1. The systemic drug exposure in both sexes increased with time in a non-linear fashion. However, in females more than dose proportional increase in AUC and drug accumulation did not translate into any systemic toxicity. The value of Tmax in both sexes increased with the dose; however, in females it was 3.4 times greater, indicating that it required a longer period to achieve a steady-state level.

Also in the previous studies, irrespective of the formulation and the drug concentration, the average topical absorption of adapalene in most species did not exceed 5 percent. The systemic absorption in rabbits was higher (14%). Following the topical applications, adapalene is mostly restricted to stratum corneum, which acts as a reservoir for drug release. However, only a small amount is released to the epidermal layers; adapalene's lipophilic properties prevent it from crossing in a significant amount to more hydrophilic layers of dermis, consequently, a very small amount is released to circulation thus limiting systemic toxicity.

Adapalene and metabolites were mainly distributed in tissues and organs involved in metabolism and excretion. Adapalene did not exhibit any affinity for lipid-rich or melanin-containing tissues or organs. In a single-dose rat study, the drug related radioactivity in amounts of (b) (4) (of the applied dose) was retained in the adrenal glands (mainly in the cortex), spleen, thymus, and ovaries. However, no such accumulation was observed upon repeated drug administration. Adapalene is extensively metabolized in animals and humans, however, its metabolic pathways and metabolites have not been properly characterized.

In rats, the placenta acted as a partial barrier to drug and its metabolites during the early sensitive period (organaogenesis) and thereafter. Adapalene is secreted in rat milk.

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption: Following a single topical dose of 0.6mg/kg [^{14}C]-adapalene, the detectable (minimum level of detection 0.15ng/mL) amounts of the parent drug were found in the plasma of mouse, rat, rabbit, and dog. A single dose topical mass balance study with 0.6mg/kg [^{14}C]-adapalene 0.1% solution under occlusion indicated absorption of 2.5 to 8% in hairless nu-ICO rats. However, the repeated daily applications of the same dose increased the absorption up to 12 percent. Among the tested species (mice, rats, rabbits, and dogs), the absorption in rabbits was greater (up to 14%). The bioavailability via the dermal route was also greater (4%) in rabbits than rats (2%). In rats, the absolute bioavailability after a single oral dose of ^{14}C-adapalene was less than 10 percent.

In a 26-week gavage study in rats, with a T_{max} of 2-3 hours, approximate bioavailabilities at dose levels of 0.15, 1.5, and 15mg/kg/day, were 75%, 17%, and 3%, respectively. In a rat teratology study with 0.1% aqueous topical gel (0.6, 2.0, and 6.0mg adapalene/kg), the bioavailability on day 10 was about 10%. In a repeated dose study (25mg adapalene/kg/day) in rabbit, the absolute bioavailability was about 1%. In a single dose oral study in beagle dogs, the systemic bioavailability of 4-5% was achieved.

Following the oral radioactive doses (0.1 and 1.0mg/kg) of adapalene to pregnant rats, the peak drug levels in the mother and fetus were achieved at 3 and 4 hours, respectively. The amount of radioactivity in the plasma of fetus at 1 hour accounted for 4% of the maternal plasma radioactivity. The $t_{1/2}$ in the mother was about 14 hours at both dose levels, while in fetus; the values were 29 and 40 hours for the low and high levels, respectively.

In the sub-chronic dermal study in minipigs (0.0, 0.2, 0.6, and 1.2mg/kg/day) with the proposed lotion formulation, the systemic absorption (Cmax) in females was 21 times greater than males; the value for $AUC_{0\text{-}24hr.}$ in females was 16.5 times greater.

No drug was detected in the plasma of women treated topically with 2g of 0.1% adapalene gel per day for 3 months. The absorption studies with excised human skin or cultured keratinocytes revealed a slightly higher absorption (never exceeding 10%) than in majority of the intact animals.

2.6.4.4 Distribution: In single and multiple-dose [^{14}C]-adapalene studies in Sprague-Dawley (S-D) rats, irrespective of the dose (0.12-0.5mg/kg), vehicle (PEG-400, CMC, or gel) or route (intravenous, oral, topical) more radioactivity was found in the plasma of females. In a 21-day rat topical study, a steady-state plasma drug level was achieved in males (0.92ng/mL) and females (1.21ng/mL) at days 8 and 13, respectively.

Following a single topical application of 0.3% adapalene solution in male S-D rats, at 24 hours post-dose, approximately 7% of the applied dose was found in the skin. Out of it 3% was present in the *stratum corneum*. It was suggested that the radioactivity diffused from the *stratum corneum* to dermis and hypodermis and also to a very limited extent (<0.1% of the dose applied) to the subcutaneous tissue. After 7 days, the amount in the

total skin was reduced to 0.1 percent. The apparent $T_{1/2}$ for elimination ranged between 3 to 4 days. In a similar study in rabbits, the corresponding amounts on days 1 and 7 were 3.5 and 1%, respectively.

In the same rat study, the micro-autographic analysis indicated that the maximum amount of radioactivity was present in the stratum corneum followed by epidermal layers surrounding the hair follicles; no radioactivity was found in dermis and hypodermis. It is suggested that the stratum corneum acts as a reservoir for drug release. However, from stratum corneum, at a time only a limited amount of adapalene reaches the epidermal layers; molecule's lipophilic properties prevent it from crossing in significant amount to more hydrophilic layers of the dermis, consequently, only a small amount of the parent drug is passed on to circulation restricting the systemic toxicity to a minimum.

In a 28-day rat topical study (0.1mg/site) with 0.1% adapalene solution, after the last application, approximately 2% of the total dose was present in the skin. The amount of radioactivity found in the tissues accounted for 0.06-0.08% of the administered dose. The elimination half-lives in the adrenals, ovaries, spleen, and uterus were much longer than plasma.

Seven days after the intravenous dose in male rats, rabbits and dogs, adrenals, liver, bile and spleen contained more radioactivity than the plasma. Each species exhibited a characteristic pattern of distribution, whereas in rat the highest amount of radioactivity was found in the adrenals, in dogs the liver and fat contained the highest amounts of radioactivity decreased rapidly in all tissues and organs, except for adrenal glands, thymus, and ovaries of rats and rabbits. The radioactivity in the adrenals was mostly retained in the cortex. However, the amount retained was very small, typically (b) (4) of the applied dose at 72 hours post-dose.

The tissue distribution data obtained from a rat dermal whole body autoradiography study revealed accumulation of drug-related radioactivity mainly in organs and tissues involved in the metabolism and excretion.

In rats, the placenta formed a relatively efficient barrier for drug and metabolite-related radioactivity after single and repeated dosing during organogenesis and upon single dosing during late pregnancy. Fetuses were exposed to less amount of drug at more sensitive early period of development than later gestation.

In vitro study with human blood, 26% of the ^{3}H-adapalene was bound to erythrocytes and the total binding in blood was more than 99%, mostly to lipoproteins and albumin.

2.6.4.5 Metabolism: Adapalene was not metabolized by reconstructed human epidermis, or after topical exposure in a rat study. This finding further supported the observed low percutaneous penetration and systemic toxicity. However, the drug was extensively metabolized by cultured hepatocytes from human, mouse, rat, rabbit, and dog. The metabolism in dogs was very similar to men. The data from several studies had indicated that metabolism probably affects only the methoxybenzene moiety. However, out of 7 fecal metabolites, only one has been identified. *In vitro* studies indicated that the major metabolite in rabbit and mouse was a glucuronide.

In 14-day rat topical (0.15-50mg/kg/day) study, adapalene did not exhibit any potential to induce or inhibit any drug metabolizing enzymes including CYP 1A, 2B, 3A, 2E, 4A, and UDP glucuronyltransferase. It confirms the findings that the drug interaction with adapalene is minimal.

2.6.4.6 Excretion: After an intravenous dose of [^{14}C]-adapalene to rats, some glucuronides, a sulfo-conjugate, and the parent drug represented 63.2, 17.1, and 19.1% of the radioactive pool in the bile. In an enterohepatic circulation study, 3-6 hours after the intravenous dose of radioactive drug into the rat duodenum, 75% of the metabolic pool was due to parent drug, while 24.1% had undergone glucuronidation; sulfonation was almost negligible. After reabsorption, the compounds were once again eliminated via the fecal route, indicating the existence of a considerable enterohepatic circulation of adapalene and its metabolites. In rats, the bile contained 79% of the administered dose, and the enterohepatic circulation was approximately 50 percent.

In all species, irrespective of route of administration, adapalene is eliminated mainly in the feces, and greater than 80% of the excretion is complete in seven days. In lactating rats, radioactivity was also excreted in the milk.

In four volunteers, the total amount of radioactivity found in the feces following a topical application of 0.1% adapalene solution amounted to 0.02-0.06% of the applied dose. No significant amount of radioactivity was found in the urine.

2.6.4.7 Pharmacokinetic drug interactions: No studies were conducted.

2.6.4.8 **Other Pharmacokinetic Studies:** N/A

2.6.4.9 Discussion and Conclusions: Irrespective of the route of administration, only a small amount of adapalene is absorbed. Minimal percutaneous penetration leads to very low systemic toxicity. The local lesions related to retinoid action of adapalene are not severe in nature. Adapalene is not metabolized in the skin. The major metabolites via other routes (oral and intravenous) are glucuronides. In multiple studies, adapalene did not exhibit any potential to induce or inhibit any drug metabolizing enzymes. Most of the drug related radioactivity (greater than 80%) is found in the bile, only a trace amount is found in the urine as polar compounds. Only 25% of the drug undergo metabolism, rest is excreted as parent drug. Most of the radioactivity is excreted within one week. Adapalene is excreted in the rat milk.

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: In adult minipigs, a four-week dose range-finding study (0.0, 0.2, 0.6, and 2.0mg adapalene/kg/day) with 0.1% lotion was followed by a 3-month dermal study. In the main study (0.0, 0.2, 0.6, and 1.2mg/kg/day), absolutely no systemic toxicity was observed at the highest dose level. On day 1, the plasma drug level was below the detection limit in all the drug treated groups. However, the repeated topical applications resulted in some drug accumulation which did not translate into any systemic toxicity. The minimal skin irritation developed at all dose levels was much reduced during the one-month recovery period. Based on the available data, the NOAEL for the systemic and dermal toxicity was considered to be 1.2mg/kg, the highest dose tested.

In the tolerance studies conducted with the 0.1% lotion, moderate dermal irritation in rabbits and delayed contact hypersensitivity occurred in guinea pigs.

The acute oral LD_{50} for adapalene in both sexes of S-D rats and CD-1 mice was greater than 5,000mg/kg. The acute LD_{50} of adapalene applied as 0.3% solution was greater than 10mL/kg (30mg/kg) in Iffa Credo OF1 male and female mice. In acute rat dermal study, 2grams/kg of 0.3% adapalene (6mg/kg/day) gel did not produce any systemic and or local toxicity.

In two separate studies where Iffa credo OF1 mice received gavage (110, 300, and 500mg /kg) and intraperitoneal doses (30, 60, and 80mg/kg) of adapalene for two weeks (10 doses), hypervitaminosis A syndrome characterized by loss of hair, body weight, spontaneous long bone fractures and skeletal resorption were observed.

The topical applications of 0.3% adapalene gel in rats at the maximum feasible dose of 2 mL/kg (6mg adapalene/kg/day) for 4-26 weeks did not cause any systemic toxicity. The dose-related lesions (scabs and acanthosis) disappeared during 8 weeks of recovery period.

In a 26-week gavage study (0.15, 1.5, and 15.0mg adapalene/kg/day) in CD rats, the drug related toxicity was restricted to a slight decrease in the number of erythrocytes in high dose females and an increase in the plasma alkaline phosphatase at the highest dose level in both sexes. Irrespective of the high plasma drug levels (7.6, 50.2, and 113.4 in males and 9.4, 46.0, 148.6ng/mL in females) after the last dose, no biological effects of any significance were observed.

Dogs treated orally (1mg/kg/day) and topically (6mg/kg/day) for 26 weeks, did not exhibit any bone-related systemic toxicity, however, epidermal hyperplasia and superficial dermal inflammation on the application sites were observed in all the topically treated animals. In another 26-week oral (1-20mg/kg/day) dog study, the changes in bones due to increased osteoclastic activity and resorption resembled hypervitaminosis A syndrome. It was inferred that 1mg oral adapalene/kg/day is close to the threshold dose that causes cranial bone changes in dogs.

Genetic toxicology: Adapalene was evaluated as non-mutagenic in gene mutation assays (Ames and mouse lymphoma tests with/without S-9 fraction), and non-clastogenic *in vitro* (Chinese hamster ovary cells with/without S-9 mix) and *in vivo* (mouse micronucleus assay at 6,000mg/kg) tests. The doses used in all the main studies were based on the dose range-finding studies, and the assays were simultaneously validated with the positive controls.

Carcinogenicity: One combined oncogenicity/chronic toxicity dietary admix study in CD rats and one dermal oncogenicity study in CD-1 mice were conducted.

In the topical study, mice received one daily application of 0.03, 0.1, and 0.3% aqueous gel (equivalent to 0.06, 2.0, and 6mg adapalene/kg/day) for 19 weeks. However, because of the severity of dermal lesions, the frequency of application was reduced to five times a week, and for the same reason was further reduced to three times per week from week 63. A number of animals were sacrificed on humane ground due to severe local reactions.

Gross pathological examination revealed thickening of the skin. The histopathologic examination indicated acanthosis, hyperkeratosis, scabs, ulcers, diffused subcutaneous inflammation, collagen deposition, atrophy of glandular and follicular structures, and increased superficial follicles in the drug treated skin. Most of these incidences were statistically significant and dose related. No drug related neoplastic changes were observed.

In the rat dietary study, animals received daily doses of 0.15, 0.5, or 1.5mg adapalene/kg/day for 104 weeks. Significant drug related non-neoplastic changes observed at 78 week interim sacrifice (chronic toxicity phase) included adrenal medullary hyperplasia in both sexes, and centrilobular hepatocytic vacuolation and extramedullary hemopoiesis in the high-dose females. The high incidences of periacinar hepatocytic fatty vacuolation, chronic inflammation of stomach, tubular mineralization of testes, and transitional cell hyperplasia of urinary bladder were observed in the high-dose males. High dose females also exhibited higher incidence of uterine dilation.

The absolute and relative weights of adrenals were significantly increased. The high-dose males exhibited a significant ($p<0.05$) incidence of benign pheochromocytoma of the adrenals. The combined number of benign and malignant pheochromocytoma, and pancreatic islet cell tumors in drug-treated males indicated a higher incidence. Accordingly, the high incidence of pheochromocytoma is a characterisitic of compounds acting like retinoids. However, there are several major morphological and biochemical differences between the adrenal glands of rat and man. Furthermore, the incidence of pheochromocytoma in man is very low (0.005 to 0.09%). A high incidence of carcinomas and adenomas of thyroid was observed in the drug treated females.

Reproductive toxicology: In rat oral reproductive performance and fertility study where F_0 female 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 rat oral teratogenicity study (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.

In segment 3 oral rat study (0.15, 1.5, and 15mg/kg/day), the highest dose of adapalene had no effect on the litter parameters (e. g. development after weaning, mating and fertility) of F_0 and F_1 generations, and on F_2 fetuses. Since adapalene was also excreted in the milk, it is inferred that the pups were exposed both *in utero* and during lactation.

Special toxicology: N/A

2.6.6.2 Single-dose toxicity: None

2.6.6.3 Repeat-dose toxicity

Study titles: 1. A 28-Day toxicity study of Adapalene Lotion, 0.1% administered dermally to minipigs.
2. A 3-Month toxicity study of Adapalene Lotion, 0.1% administered dermally to minipigs with a 1-month recovery period.

Key study findings: In the main study, irrespective of some indication for drug accumulation especially in the high-dose females, no systemic toxicity was observed. The minimal skin irritation (erythema) observed in all groups including vehicle, diminished during the recovery phase. The systemic and dermal NOAEL was considered to be 1.2mg/kg/day.

Study nos.: NHM00097 and NHM00098
Volume #, and page #: N/A
Conducting laboratory and location: (b) (4)
Dates of study initiation: 17 September 2007 and 15 January 2009
GLP compliance: Yes
QA report: yes
Drug, lots #, and % purity: Lots LB-07134; 052282 and 052310

Methods

Doses:

Study 1: 0.0 (Gp1, vehicle control), 0.2 (Gp2), 0.6 (Gp3), 2.0 (Gp4) mg adapalene/kg

Study 2: 0.0 (Gp1, sham control), 0.0 (Gp2, vehicle control),

0.2 (Gp3, low-dose), 0.6 (Gp4, mid-dose), 1.2mg adapalene/kg/day (Gp5, high-dose)
Species/strain: Male and female Gottingen minipigs
Number/sex/group or time point: one/sex for study 1
6/sex for study 2
Route, formulation, volume, and infusion rate:
Topical, lotion
Study 1: 2.0, 0.2, 0.6, or 2mL of lotion/kg/day
Study 2: 0.0, 0.0, 0.2, 0.6 or 1.2mL of lotion/kg/day

Satellite groups used for toxicokinetics or recovery:
Study 2: 2/sex in groups 2 and 5
Age: Study 1: 21-23 weeks Study 2: 11-15 weeks
Weight: Study 1: Males, 10.05-11.09kg; Females, 10.68-11.86kg
Study 2: Males, 6.75-9.54kg; Females, 7.58-9.39kg
Sampling times: Blood samples: only in the second study
Clinical pathology: Samples from all animals were collected on day 3, and day 92/93. Samples from recovery animals (groups 2 and 5) were collected on day 120.
Toxicokinetics: Samples from all animals were collected on days 1 and 91 at 0, 1, 2, 4, 7, and 24 hours post-application.

Unique study design or methodology (if any): The first study was aimed to select doses expected to produce graded toxicological responses. Animals received topical applications of drug product/vehicle on days 1-28 in study 1, and on days 1-91/92 in the second study. The area of application for each animal was calculated once a week using Spector's formula for 6-30 kg pigs (Spector, W.S. Handbook of Biological Data. Philadelphia: W.B. Sander Company 1956; 175). Each exposure was maintained for 23-24 hours. The marked application sites were covered with stockinette (non-occlusive binding) sleeves.

Observations/determinations/Results

Mortality: Animals were examined twice daily for clinical signs of toxicity, morbidity and mortality.

No unscheduled deaths were recorded in either of the studies.

Clinical signs: In both studies, detailed examinations for systemic and dermal toxicity were conducted prior to initiation of drug treatment and weekly thereafter.

No systemic toxicity was observed in either of the studies. In the dose range-finding study, the vehicle related dermal reactions were restricted to slight edema and desquamation. Additional dermal lesions such as slight to severe erythema, very slight to slight edema, desquamation, skin sloughing, focal and or pinpoint areas of eschar, and

eschar exfoliation, were mainly observed in the high-dose animals (2mg/kg/day). Erythema at all dose levels was extended beyond the application site.

Based on the diversified and high intensity dermal lesions observed in the 28-day study, the highest dose volume in the main study was reduced to 1.2mL/kg.

In the 90-day study, dermal lesions such as very slight erythema and edema and minimal eschar formation were observed in all groups including vehicle control. The pronounced increase in erythema was dose related, however, the rate of incidence was similar in the vehicle control and the high-dose animals.

During the recovery phase, a few animals in the drug treated and vehicle groups had slight erythema.

Body weights: Individual body weights in both studies were determined on day 3 and weekly thereafter.

In both studies, no intergroup differences in body weights were recorded. A few scattered but statistically significant changes (increases/decreases) did not exhibit any dose or sex related trend, and therefore, were not considered biologically significant.

Food consumption: Food consumption was not recorded.

Ophthalmoscopy: No Ophthalmic examinations conducted were conducted in the dose range-finding study. Examinations conducted prior to study initiation and on day 90 in the main study, did not reveal any changes in the eye morphology.

EKG: Electrocardiograms were recorded for all animals on days 5, 87, and 115 (recovery phase). Measurements were obtained using leads I, II, III, aV_R, aV_L and V_F at a chart speed of 50mm/second. Blood pressures were also recorded on the same time points.

Throughout the study period, no drug related changes in the blood pressure or electrocardiograms were observed.

Hematology/Clinical chemistry: Blood samples from all animals were used to determine16 hematological, activated PTT coagulation test, and 19 clinical chemistry parameters.

No statistically significant changes in any parameters were recorded.

Urinalysis: Samples collected from all animals by cystocentesis at necropsy were used to evaluate 14 major parameters.

No statistically significant changes in any parameters were recorded.

Gross pathology: All the treatment and recovery phase animals were subjected to extensive necropsy examination including evaluation of carcasses, musculoskeletal system, all the external surfaces and orifices, cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

The sporadically distributed gross lesions such as epididymides cyst (1/4 mid-dose males) and its discoloration (1/4 mid- and high-dose males), small gallbladder (1/4 high-dose males), and dark discoloration of lung (1/4 high-dose females) were not considered drug or treatment related.

Organ weights: Absolute and relative to body and brain weights were determined for the following organs: Adrenal glands (paired), brain, epididymis (paired), heart, kidneys (paired), liver, lung, ovaries (paired), pituitary gland, salivary glands (paired), spleen, testis (paired), thymus, thyroid glands (paired), and the uterus.

No statistically significant changes in the organ weights occurred in males. In the mid-dose females, a statistically significant increase in the absolute and relative to body weights of brain was recorded; however, no such increase was observed in the high-dose females.

Histopathology: Adequate Battery: yes Peer review: yes

A total of 47 organs/tissues from each animal were processed and subjected to microscopic examinations.

Microscopic dermal lesions such as epidermal vacuolation, increased chronic inflammation and rare epidermal degeneration were observed at all the dose levels. However, no dose-related trends in severity or frequency of occurrence were recorded. Similar vacuolar lesions were also observed in the sham and vehicle controls. At the end of recovery phase, severity and frequency of all the lesions were much diminished.

Toxicokinetics: On day 1, the plasma drug level in all groups of both sexes was below the detection limit. The systemic exposure in both sexes increased with the dose over time in a non-linear fashion (Table1). However, in females more than dose proportional increase in Cmax and $AUC_{0\text{-}24hr}$ suggested some drug accumulation. It must be mentioned that the greater plasma drug levels in the high-dose animals did not translate into any systemic toxicity. The values of Tmax at the low- and mid-dose levels were similar in both the sexes; however, values were much greater at the high-dose level especially in females where it was 3.4 times greater than males. It indicated that females probably required more time to achieve a steady state.

Table 1. A summary of toxicokinetic data at 24 hours post-dose on day 91

Dose (mg/kg/day)	0.2		0.6		1.2	
Sex	M	F	M	F	M	F
Parameter						
Cmax (ng/mL)	0.47	0.41	2.70	1.10	1.16	24.37
Tmax (hr.)	4.00	4.00	4.00	3.50	7.00	24.00
AUC_{0-24h}	9.25	4.31	56.89	12.86	18.39	304.26

2.6.6.4 Genetic toxicology: No studies were conducted with DIFFERIN (adapalene) Lotion, 0.1%

2.6.6.5 Carcinogenicity: No studies were conducted with DIFFERIN (adapalene) Lotion 0.1%

2.6.6.6 Reproductive and developmental toxicity: No studies were conducted with DIFFERIN (adapalene) Lotion 0.1%

2.6.6.7 Local tolerance: Two studies (primary dermal irritation in rabbits, and delayed contact hypersensitization in guinea pigs) conducted with 0.1% lotion were reviewed under IND 76,057.

The 0.1% lotion tested as a moderate dermal irritant in rabbits, and caused delayed contact hypersensitivity in guinea pigs.

2.6.6.8 Special toxicology studies: No studies were required or recommended.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

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

In pharmacology studies, adapalene exhibited retinoid-like activities such as modulation of cellular differentiation and keratinization. However, some pharmacodynamic differences separate adapalene from tretinoin. First, although adapalene binds to specific retinoic acid nuclear receptors (RARγ, RARß, and RARγ), the affinity of adapalene for RARα is much lower than tretinoin. 9-*cis*-retinoic acid has been established as a physiologic ligand of tretinoin, not adapalene. Second, unlike tretinoin, adapalene does not bind to cellular retinoid binding protein II (CRAB II). Possibly, due to these

differences, the dermal lesions caused by retinoid like biological activity of adapalene are not severe. Furthermore, such lesions were observed at high oral doses.

The 0.3% combination gel (0.125, 0.250, and 0.750mg adapalene/animal) did not alter any cardiovascular functions in the 13-week minipig dermal study.

Safety pharmacology studies to support the previously approved topical formulations were conducted at much higher dose levels. Thus, 100mg/kg of oral adapalene did not alter the behavior, physical health, and spontaneous locomotor activity, hexobarbital sleeping time, pain response, basal tone ileum, and gastrointestinal motility in mice. At the same dose level, functioning of cardiovascular, respiratory, and central nervous systems in dogs, and urine volume and electrolyte excretion in rats were not altered.

In the sub-chronic dermal minipig study (0.0, 0.2, 0.6, and 1.2mg/kg/day) conducted with the 0.1% lotion formulation, no cardiotoxicity or changes in electrocardiograms or blood pressure were recorded. In the same study, absolutely no systemic toxicity and minimal reversible skin irritation was observed. The NOAEL was appropriately established at the highest dose tested.

In local tolerance assays, the 0.1% lotion caused moderate skin irritation in rabbits and delayed contact hypersensitivity in guinea pigs.

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

Adapalene has also been evaluated for systemic and local toxicity at level three times greater that present in the lotion formulation. Thus, the topical application of 0.3%adapalene gel in rats at the maximum feasible dose of 2mL/kg (36mg adapalene/m^2/day) for 4-26 weeks did not cause any systemic toxicity. The dose-related scab formation and acanthosis disappeared during 8 weeks of recovery period. Dogs treated topically (120mg/m^2/day) for 26 weeks did not exhibit any bone-related systemic toxicity; and the epidermal hyperplasia and superficial inflammation developed on the application sites were transient and mild in nature.

Irrespective of the nature of the formulation and or the drug concentration, the average topical absorption of adapalene in most species including humans did not exceed 5 percent. No significant drug accumulation was observed in the dermal studies of any duration. Adapalene is extensively biodegraded in animals and humans, and the parent drug and metabolites are mainly found in organs (liver, GI-tract) involved in the excretory metabolism. Adapalene did not exhibit any affinity for lipid-rich or melanin containing tissues or organs (skin, hair, and eyes).

Adapalene was established as non-genotoxic in a battery of *in vitro* and *in vivo* assays. The drug also tested non-carcinogenic in mice dermal study. In rat oral carcinogenicity study, a higher incidence of benign pheochromocytomas of the adrenal glands was reported. However, the relevance of this finding to humans is unknown.

Adapalene like other retinoids could induce teratogenicity at sufficiently high systemic doses (oral doses from 25mg/kg/day). A dermal NOAEL of 36 and 72mg/m^2/day was established in rat and rabbit embryo-toxicity studies, respectively. Furthermore, during a decade of extensive global use of 0.1% adapalene preparations, not a single case of teratogenicity in humans has been reported.

Unresolved toxicology issues (if any): None

Recommendations: The non-clinical safety of DIFFERIN (adapalene) Lotion 0.1% is well established, therefore, I have no objection to the approval of this New Drug Application.

Suggested labeling:

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

2 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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

/s/

DAIVENDER K MAINIGI
09/17/2009

BARBARA A HILL
09/17/2009

Filability of NDA 022502

Division of Dermatologic and Dental Drug Products (HFD-540) Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date: 04-08-2009
Reviewer: Kumar D. Mainigi
NDA Number: 022502
Drug Name: Adapalene Lotion 0.1%
CAS Number: 106685-40-9
Drug Type: 3S
Drug Class: Napthoic acid class of anti-acne agent
Indication: Treatment of acne vulgaris
Route of Administration: Topical
Date CDER Received: March 2, 2009
User Fee Date: January 1, 2010
Date of Draft Review: July 2, 2009
Sponsor: Galderma Laboratories

Fileability: On initial overview of the NDA application:

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed? **Yes**

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review? **Yes**

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed? **Yes**

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies etc)? **Yes**

(5) If the formation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? **N/A**

(6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? **Yes**

(7) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? **Yes**

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route? **Yes**

(9) Has the sponsor submitted a statement (s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? **Yes**

(10) Has the sponsor submitted the data from the non-clinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometerics? **N/A**

(11) Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of other art protocols which also reflect agency's animal welfare concerns? **Yes**

(12) From pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. **Yes**

(13) If the NDA is fileable, are there any issues that need to be conveyed to sponsor? If so specify: **No**

(14) Issues that should not be conveyed to the sponsor: **N/A**

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

/s/

Kumar Mainigi
5/4/2009 08:46:02 AM
PHARMACOLOGIST

Barbara Hill
5/4/2009 08:46:51 AM
PHARMACOLOGIST