NDAs 20-338
20-380

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PP1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-338

MAY 31 1996

Galderma Laboratories, Inc.
Attention: Ms. Christine E. Shank
Manager Regulatory Affairs
P.O. Box 331329
Fort Worth, Texas 76163

Dear Ms. Shank:

Please refer to your March 19, 1993, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Differin (adapalene solution), Solution, 0.1%.

We acknowledge receipt of your amendments and correspondence dated April 29, May 6 and 21, June 9 and 22, July 1 and 20, August 12 and 27, September 17 and 24 (two), October 29 (two), November 1 and 24, and December 3 and 10, 1993; January 10, 17, and 31, February 28, March 2 and 18, April 1, 4, and 26, June 3 and 15, September 2, and November 10, 1994; January 11, February 21, March 21, May 1, and July 6, 1995; and May 30, 1996.

This new drug application provides for the topical treatment of acne vulgaris.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling submitted on May 30, 1996. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the May 30, 1996, draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight-paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved NDA 20-338." Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Dermatologic and Dental Drug Products, and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions concerning this application, please contact:

Mary Jean Kozma-Fornaro, RN, MSA
Project Manager
Telephone: (301) 827-2020

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-338
HFD-540/Div File
HF-2/MedWatch(w/labeling)
HFI-20/Kupec(w/labeling)
HFD-2/CDER DEP DIR/MLumpkin(w/labeling)
DAL-DO
HFD-105(w/labeling)
HFD-102(w/labeling)
HFD-613(w/labeling)
HFD-80(w/labeling)
HFD-40/w/labeling)
HFD-735(w/labeling)
HFD-222/New Drug Chemistry Division Director
HFD-540/DIV DIR/Wilkin
HFD-540/DEP DIR/Katz
HFD-550/ACT DIV DIR/Chambers WAC 5/31/96
HFD-520/Bostwick
HFD-520/CHEM/Timper
HFD-540/PHARM/Mainigi
HFD-520/MICRO/Dionne
HFD-713/BIOSTAT/Chakravarty
HFD-880/BIOPHARM/Dorantes
HFD-540/PROJ MGR/Fornaro

Concurrence:

HFD-540/PHARM TEAM LEADER/Jacobs
HFD-540/CHEM TEAM LEADER/DeCamp
HFD-540/SPMS/Cook
HFD-880/BIOPHARM TEAM LEADER/Pelsor
HFD-520/MICRO TEAM LEADER/Sheldon
HFD-713/DIR/Harkins

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APPROVAL

Draft

MAY 31 1996

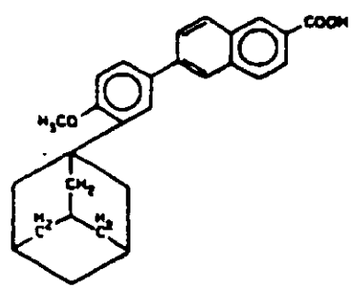
May 30, 1996
NDA 20-338

GALDERMA LABORATORIES, INC. - Final Draft Labeling text for the physician package insert for DIFFERIN™ (adapalene solution) Solution, 0.1%.

DIFFERIN™
(adapalene solution)
Solution, 0.1%

DESCRIPTION: DIFFERIN™ Solution, containing adapalene, is used for the topical treatment of acne vulgaris. Each mL of DIFFERIN Solution contains adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula:



CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is

unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Pharmacokinetics: Absorption of adapalene through human skin is low. Only trace amounts (< 0.25 ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.

INDICATIONS AND USAGE: DIFFERIN Solution is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: DIFFERIN Solution should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle solution.

WARNINGS: Use of DIFFERIN Solution should be discontinued if hypersensitivity to any of the ingredients is noted. Patients with sunburn should be advised not to use the product until fully recovered.

PRECAUTIONS: ***General:*** If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.

Drug Interactions: As DIFFERIN Solution has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN Solution. If these preparations have been used, it is advisable not to start therapy with DIFFERIN Solution until the effects of such preparations in the skin have subsided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4-75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.

No photocarcinogenicity studies were conducted. Animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

In a series of *in vivo* and *in vitro* studies, adapalene did not exhibit mutagenic or genotoxic activities.

Pregnancy: Teratogenic effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5.0 mg/kg/day, up to 120 times the maximal daily human topical dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose 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.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS: Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 30-60% of patients. Pruritus or burning immediately after application also occurs in approximately 30% of patients. The following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN Solution during clinical trials were reversible upon discontinuation of therapy.

OVERDOSAGE: DIFFERIN Solution is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. The acute oral toxicity of DIFFERIN Solution in mice and

rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: DIFFERIN Solution should be applied once a day to affected areas after washing in the evening before retiring. A thin film of the solution should be applied, avoiding eyes, lips, and mucous membranes.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

HOW SUPPLIED: DIFFERIN (adapalene solution) Solution, 0.1% is supplied in the following sizes:

30 mL glass bottle with applicator - NDC 0299-5905-30

60 mL glass bottle with applicator - NDC 0299-5905-60

The applicator is designed so that the solution may be applied directly to the involved skin.

Storage: Store at controlled room temperature 20° - 25°C (68° - 77°F). Keep container tightly closed and store upright.

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:
GALDERMA Laboratories, Inc.
Fort Worth, Texas 76133 USA

Mfd. by:
DPT Laboratories, Inc.
San Antonio, Texas 78215 USA

Revised: May 1996

Physician Package Insert

DIFFERIN™

(adapalene)

Solution, 0.1%

DESCRIPTION: DIFFERIN™ Solution, containing adapalene, is used for the topical treatment of acne vulgaris. Each mL of DIFFERIN Solution contains adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula:

CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, current evidence suggests that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Studies in acne patients provide clinical evidence that topical adapalene is effective in reducing the noninflammatory acne lesions. In both *in vivo* and *in vitro* assay models, adapalene exhibits anti-inflammatory activity and studies in acne patients provide clinical evidence that topical adapalene is also effective in reducing the inflammatory components of acne (i.e., papules and pustules).

Pharmacokinetics: Absorption of adapalene through human skin is low. No quantifiable levels (limit of quantification = 0.25 ng/mL, of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.

INDICATIONS AND USAGE: DIFFERIN Solution is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: Use of the product should be discontinued if hypersensitivity to any of the ingredients is noted.

PRECAUTIONS: *General*: If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure; and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose and mucous membranes. The product should not be applied to cuts, abrasions or eczematous skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen as the skin "accommodates" to this medication. Depending upon the

severity of side effects, patients should be instructed to reduce the frequency of application or discontinue use.

Drug Interactions: As DIFFERIN Solution has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol or salicylic acid in combination with DIFFERIN Solution. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before initiating therapy with DIFFERIN Solution. A study conducted with DIFFERIN Solution, however, has demonstrated that concurrent therapies such as erythromycin topical solution 4%, clindamycin phosphate topical solution 1% or benzoyl peroxide products in concentrations up to 10% do not cause any additive irritant effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime studies with adapalene have been completed in mice at topical doses of 0.6, 2 and 6 mg/kg/day and in rats at oral doses of 0.15, 0.5 and 1.5 mg/kg/day and demonstrated no carcinogenic effect. Some animal studies have shown an

increased tumorigenic risk with the use of related drugs when combined with exposure to the ultraviolet (UV) light in sunlight, or from other UV sources. Although the significance of these studies to man is not clear, patients should avoid or minimize exposure to sunlight. Adapalene is essentially stable to oxygen and light and studies in animals and humans have shown no phototoxic or photoallergic potential. Studies to determine whether adapalene may accelerate the tumorigenic effects of UV radiation have not been conducted.

In a series of *in vivo* and *in vitro* animal tests, adapalene did not demonstrate mutagenic or genotoxic activity. Reproductive function and fertility studies were conducted in rats administered oral doses of adapalene in amounts up to 20 mg/kg/day. No effects of adapalene were found on the reproductive performance or fertility of the F_0 males or females. There were also no detectable effects on the growth, development and subsequent reproductive function of the F_1 offspring.

Pregnancy: Teratogenic effects. Pregnancy Category C. *Oral*. Adapalene, like all retinoids and Vitamin A, at high oral doses (5 mg/kg or greater) corresponding to at least 125 to 500 times the expected maximum human daily dose (assuming a 50 kg adult applies 0.5 g to 2 g of 0.1% solution topically) is teratogenic in rats and rabbits. *Topical*. Teratology studies

performed in rats and rabbits at cutaneous doses from 50 to 200 times the human dose (assuming the human dose to be 0.5 g to 2.0 g of 0.1% solution per day) have shown no evidence of effects on the fetus *in utero* in the rabbit, and only a minimal increase in supernumerary ribs in rats, which are considered to be of no toxicological, functional or teratological significance. 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.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: In clinical trials with DIFFERIN Solution, the total incidence of adverse reactions was 14.5% (83 reports from 571 participants). The most frequent adverse reactions reported were burning and stinging (3.7%), skin irritation (2.4%), erythema (2.1%), dry skin (1.9%), sunburn (1.6%) and pruritus (1.4%). Other adverse experiences which were

attributed to treatment but occurred less frequently (in less than 1% of patients) were dermatitis, acne flare and one instance of impetigo flare. Most of the reactions occurred within two to four weeks of initiation of therapy and were generally observed to resolve with continued use of the product or temporary adjustment of the treatment schedule. All adverse effects with use of DIFFERIN Solution during clinical trials were reversible upon discontinuation of therapy.

Some degree of side effects such as erythema, scaling, dryness, pruritus and burning will occur in 30-60% of patients. Pruritus or burning immediately after application also occurs in approximately 30% of patients. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter.

OVERDOSAGE: DIFFERIN Solution is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur. The acute oral toxicity of DIFFERIN Solution in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: DIFFERIN Solution should be applied to the skin where acne lesions appear once a day before retiring and after washing. A thin film of the solution should be applied, avoiding eyes, lips and mucous membranes.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after two weeks with definite beneficial effects evident after four weeks.

Patients should be advised to use non-comedogenic cosmetics.

HOW SUPPLIED: DIFFERIN (adapalene) Solution is supplied in the following sizes:

30 mL glass bottle with applicator - **NDC** 0299-5905-30

60 mL glass bottle with applicator - **NDC** 0299-5905-60

The applicator is designed so that the solution may be applied directly to the involved skin.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Keep container tightly closed and store upright.

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:

Galderma Laboratories, Inc.
Fort Worth, Texas 76133 USA

Mfd. by:

DPT Laboratories, Inc.
San Antonio, Texas 78215 USA

GALDERMA is a registered trademark.

Revised: May 1994

30 mL BOTTLE LABEL

Principal Display Panel

NDC 0299-5905-30

DIFFERIN™ Solution 0.1%
(adapalene)
Topical Solution

CAUTION: Federal law prohibits dispensing without prescription.

OWEN/GALDERMA (Logo)

30 mL

Information Panel

For External Use Only. Not For Ophthalmic Use.

Store at controlled room temperature 15°-30°C (59°-86°F).

Keep container tightly closed and store upright.

Usual dosage: Apply a thin film to affected areas once a day, before retiring. See package insert for complete prescribing information.

Each mL contains: adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

Lot number and expiration date printed on bottom of bottle.

Marketed by:

OWEN/GALDERMA Laboratories, Inc.

Fort Worth, Texas 76134 USA

Mfd. by:

DPT Laboratories, Inc.

San Antonio, Texas 76215 USA

OWEN and GALDERMA are registered trademarks.

(part number and date code)

30 mL CARTON

Principal Display Panel

NDC 0299-5905-30

DIFFERIN™ Solution 0.1%
(adapalene)
Topical Solution

CAUTION: Federal law prohibits dispensing without prescription.

OWEN/GALDERMA (Logo)

30 mL

Back Information Panel

For External Use Only. Not For Ophthalmic Use.

Store at controlled room temperature 15°-30°C (59°-86°F).

Keep container tightly closed and store upright.

Usual dosage: Apply a thin film to affected areas once a day, before retiring. See package insert for complete prescribing information.

Each mL contains: adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

Marketed by:

OWEN/GALDERMA Laboratories, Inc.

Fort Worth, Texas 76134 USA

Mfd. by:

DPT Laboratories, Inc.

San Antonio, Texas 76215 USA

(part number and date code)

Side Information Panel

To install enclosed applicator:

1) Remove cap from bottle and discard.

2) Remove applicator from overwrap, position on bottle and press firmly into place.

3) Seal firmly by tightening applicator cap.

Top Tuck Flap

DIFFERIN™ Solution 0.1%
(adapalene)
Topical Solution

30 mL

Bottom Tuck Flap

Lot:

Expires:

60 mL BOTTLE LABEL

Principal Display Panel

NDC 0299-5905-60

DIFFERIN™ Solution 0.1%
(adapalene)
Topical Solution

CAUTION: Federal law prohibits dispensing without prescription.

OWEN/GALDERMA (Logo)

60 mL

Information Panel

For External Use Only. Not For Ophthalmic Use.

Store at controlled room temperature 15°-30°C (59°-86°F).

Keep container tightly closed and store upright.

Usual dosage: Apply a thin film to affected areas once a day, before retiring. See package insert for complete prescribing information.

Each mL contains: adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

Lot number and expiration date printed on bottom of bottle.

Marketed by:

OWEN/GALDERMA Laboratories, Inc.

Fort Worth, Texas 76134 USA

Mfd. by:

DPT Laboratories, Inc.

San Antonio, Texas 76215 USA

OWEN and GALDERMA are registered trademarks.

(part number and date code)

60 mL CARTON

Principal Display Panel

NDC 0299-5905-60

DIFFERIN™ Solution 0.1%
(adapalene)
Topical Solution

CAUTION: Federal law prohibits dispensing without prescription.

OWEN/GALDERMA (Logo)

60 mL

Back Information Panel

For External Use Only. Not For Ophthalmic Use.

Store at controlled room temperature 15°-30°C (59°-86°F).

Keep container tightly closed and store upright.

Usual dosage: Apply a thin film to affected areas once a day, before retiring. See package insert for complete prescribing information.

Each mL contains: adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

Marketed by:

OWEN/GALDERMA Laboratories, Inc.

Fort Worth, Texas 76134 USA

Mfd. by:

DPT Laboratories, Inc.

San Antonio, Texas 76215 USA

(part number and date code)

Side Information Panel

To install enclosed applicator:

1) Remove cap from bottle and discard.

2) Remove applicator from overwrap, position on bottle and press firmly into place.

3) Seal firmly by tightening applicator cap.

Top Tuck Flap

DIFFERIN™ Solution 0.1%
(adapalene)
Topical Solution

60 mL

Bottom Tuck Flap

Lot:

Expires:

MOR

APR 11 1996

Supervisory Medical Officer's Review of NDA 20-338

NDA 20-338

Review completed: 7/ 5/94

Drug name: Differin Solution, 0.1%
Generic name: Adapalene solution

Sponsor: Owen/Galderma Laboratories, Inc.
Fort Worth, TX 76115

Pharmacologic Category: "Retinoid-like"

Proposed Indication(s): Treatment of acne vulgaris

Related Reviews: Clinical Review dated 10/ 7/93
Clinical Addendum dated 3/30/94

Background:

The clinical review recommends potential approval from a clinical prospective while identifying differences between studies in the efficacy rates of the test product.

Differences between studies in the safety profile (including adverse experiences) were also noted.

Clinical Studies:

1. Skin Irritation Test — M. Verschoore — France

Reviewer's Comments: *Concur with primary review, the study was inadequate to establish the irritancy potential of 0.1% adapalene solution. Study needed additional patients and a study arm with a reference product of known low irritancy.*

2. Sensitization Test — M. Verschoore — France

Reviewer's Comments: *Concur with primary review that this study demonstrated a low degree of irritancy, however, there is disagreement concerning the adequacy of the study to establish that it is not a sensitizer. The study has only half the number of patients usually evaluated in a sensitization study.*

3. Phototoxicity L. Duteil France

Reviewer's Comments: *No phototoxicity reactions were observed.*

4. Photoallergic Contact Sensitization L. Duteil France

Reviewer's Comments: *No reactions seen during the challenge phase.*

5. Skin Irritation C. Raybaut France

Reviewer's Comments: *Concur with primary review that the study fails to establish the irritancy potential because occlusion was not used on the test sites.*

PC 86019 11 patients.

2 drop outs due to ADR (1-irritation, 1-erythema, pruritus, burning)

Other ADRs- Pruritus (5/9), Burning (4/9), Dry skin (1/9). Only one case of burning and pruritus in the vehicle group.

PC 86013 10 patients.

ADRs- Dryness (9/10), erythema (6/10), burning (3/10), pruritus (2/10). Only half as many reactions in the vehicle group.

PC 86012 10 patients.

ADRs- Dry skin (7/10), pruritus (7/10), erythema (6/10), burning (5/10). No reactions in the vehicle group.

Reviewer's Comments: *The adverse experiences observed in the initial studies suggest a significant irritancy potential and an unknown sensitization potential. As noted in the primary clinical review, serious question has been raised concerning the use of adapalene solution for acne on the back.*

Efficacy: (Summary of Larger Studies)

STUDY		% Reduction at Endpoint			
		Adapalene	Tretinion	Retin-A	Vehicle
C-88-27	Non-inflammatory lesions	33%			28%
	Inflammatory lesions	6%			8%
	Global Grade	34%			31%
9104-CD271L-EV	Non-inflammatory lesions	34%			12%
	Inflammatory lesions	28%			28%
	Global Grade	25%			13%
PH 87027	Non-inflammatory lesions	66%	66%		
	Inflammatory lesions	50%	50%		
	Global Grade	50%	33%		
C-88-26	Non-inflammatory lesions	55%		52%	
	Inflammatory lesions	46%		45%	
	Global Grade	24%		26%	
CR 88043	Non-inflammatory lesions	72%		70%	
	Inflammatory lesions	62%		66%	
	Global Grade	50%		50%	

Reviewer's Comments: *The vehicle controlled studies showed significantly less effective results than the active controlled studies. Of the vehicle controlled studies, only one shows a statistically significant difference from vehicle (and only in non-inflammatory lesions).*

It is recommended that an additional vehicle controlled study be performed. At the very least, the applicant should provide an explanation for the discrepancies.

Recommendations

NDA 20-338, Differin (adapalene solution), 0.1% is not recommended for approval until the following deficiencies are satisfactorily addressed by the applicant:

1. The vehicle controlled studies showed significantly less effective results than the active controlled studies. An explanation for the discrepancies in efficacy rates must be provided. It is recommended that this be addressed by performing an additional vehicle controlled study.

2. The sensitization study did not include enough patients to adequately evaluate the potential for sensitization. It is recommended that an additional sensitization study be performed in at least 200 patients.

3. The initial studies have raised concern over the use of adapalene solution for acne on the back. A specific justification, including safety and efficacy evaluations should be provided if this claim is to be retained.

4. The application does not contained any support for the treatment of inflammatory lesions. Efficacy support is needed if this claim is to be retained.

5. The initial studies showed high rates of erythema, dryness, burning and pruritus. There is a discrepancy between these initial studies and the reported rates of the phase 3 clinical trials. An explanation should be provided.

A final labeling review will be completed after the above deficiencies are addressed.

Wiley A. Chambers MD
Wiley A. Chambers, M.D.
Supervisory Medical Officer

4/11/94

cc: HFD-540
HFD-340
HFD-540/CSO/~~Cook~~ FORNARO
HFD-520/CHEM/Timper
HFD-540/PHARM/Mainigi
HFD-520/MO/Bostwick
HFD-540/SMO/Chambers
HFD-713/STAT/Daphne
HFD 540 - TOOMBS

APR 11 1996

Date Review Initiated: August 16, 1993
Date Completed: October 7, 1993

Clinical Review of NDA 20-338

Original Submission

Sponsor: Owen/Galderma Laboratories, Inc.
P.O. Box 6600
Fort Worth, TX 76115

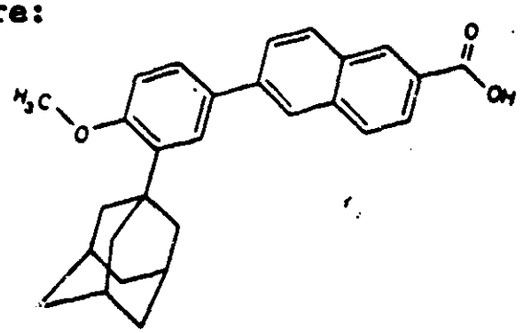
Drug: Differin (adapalene) Solution, 0.1%.

Date of Submission: March 19, 1993. Amendments dated May 6, June 22, August 27, and September 17, 1993.

Formulation:

Component	Quantity (w/w%)
Adapalene	0.1
Polyethylene glycol 400	
SD Alcohol 40-B	

Adapalene is a "retinoid-like" compound, with the following chemical structure:



Indication: Differin Solution is indicated for the topical treatment of acne vulgaris.

Dosage and Administration: Following is the sponsor's proposed Dosage and Administration section of the labeling:

"**DOSAGE AND ADMINISTRATION:** DIFFERIN Solution should be applied to the affected areas of the face, chest and back once a day before retiring and after washing. A thin film of the solution should be applied, avoiding eyes, lips and mucous membranes.

Clinical improvement is expected to be clearly evident after four to eight weeks of treatment, with further improvement expected with continued use. Cutaneous safety of DIFFERIN Solution has been demonstrated over a one-year period of treatment.

With patients for whom it is necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be

resumed or frequency of application increased if it is judged that the patient is able to tolerate the treatment.

Patients should be advised to use non-comedogenic cosmetics. Color cosmetics such as blushers and powders are acceptable, however, make-up cosmetics should be water based only."

Packaging: The product is to be packaged in 30 mL and 60 mL applicator-tipped bottles.

Microbiology Review: In his reviews dated May 4 and June 4, 1993, the reviewing microbiologist, Dr. Dionne, recommended that the application be approved.

Chemistry Review: In his review dated May 5, 1993, the reviewing chemist, Mr. Timper, recommended that this application not be approved because of deficiencies in stability, methods validation, labeling and laboratory controls. A decision has not yet been made on whether to accept the proposed trade name (Differin).

Statistical Reviews: In the statistical review dated November 2, 1993 by Dr. Chakravaty (addendum by Dr. Srinivasan), the Biometrics staff found the application approvable in that the active product is superior to the vehicle in the treatment of non-inflammatory and total lesions, and is equivalent to Retin-A in all lesion types.

Other Reviews: The pharmacology and biopharmaceutics reviews are not yet available.

Related Submissions: The studies presented in this NDA were performed under IND Owen/Galderma recently submitted an NDA for Differin (adapalene) Gel, 0.1% (NDA 20-380).

Background: Adapalene is a new chemical entity which has never been approved in the U.S. or anywhere else in the world. Drug development and pre-clinical studies were done by Galderma in Valbonne, France. Phase 1 clinical studies were also done in Europe, while Phase 2 and 3 clinical studies were done in both Europe and the U.S.

Adapalene is a naphthoic acid derivative whose chemical structure has elements of the retinoid structure. In addition to the activities commonly seen in topically applied retinoids (cellular turnover and comedolytic), the sponsors state that adapalene has demonstrated anti-inflammatory activity in animal models, which would give it activity against both inflammatory (papules, pustules) and non-inflammatory (comedones) acne lesions.

In assays for retinoid-like activities in animals, adapalene performed better than topically applied isotretinoin (Accutane)

and etretinate (Tegison), but not as well as tretinoin (Retin-A). Animal anti-inflammatory activity was superior to all three reference retinoids.

Orally administered adapalene is teratogenic in rats and rabbits, but topical doses 50-200 times the human dose demonstrated no effects in rabbits and only an increase in supernumerary ribs in rats.

Material Reviewed: The sponsor has submitted the following studies in support of the safety and efficacy of this product:

1. Pharmacokinetics and bioavailability (to be reviewed by FDA's Biopharmaceutics staff).

2. Studies to assess the irritation, sensitization, phototoxicity and photoallergy potential of the drug formulation.

3. A percutaneous absorption study (also included in the pharmacokinetics and bioavailability section noted above).

4. Six vehicle-controlled studies as follows:

    a. 30 male patients (Jablonska) - parallel groups.

    b. 110 patients of both sexes (Jones, Kantor, Swineheart, Greenspan) - parallel groups.

    c. 243 patients of both sexes (Ast, Cullen, Dunlap, Hickman, Lucky, Potter, Rapaport, Stoughton) - parallel groups.

    d. 3 small bilateral paired-comparison studies of 10 patients each.

5. A dose-ranging comparing 0.1% and 0.03% adapalene solutions to 0.025% tretinoin gel. 41 patients in parallel groups.

6. Two positive-controlled studies, as follows:

    a. 297 patients of both sexes - 0.1% adapalene vs. 0.025% tretinoin gel (Smith, Millikan, Swinyer, Ellis, Katz, Berger, Chalker, Leaderman) - parallel groups.

    b. 245 patients of both sexes - 0.1% adapalene vs. 0.025% tretinoin gel (Cunliffe, Jones, MacDonald, Orfanos, Privat, Amblard,

Brunetiere, Caputo, de la Brassine) - parallel groups.

For convenience, the review of the clinical data will be organized as follows:

A. Dermatotoxicity Studies (including the percutaneous absorption study)

B. Vehicle Controlled Studies

C. Positive Controlled Studies (including the dose-ranging study)

D. Safety Summary

E. Labeling Review

There will be an efficacy summary and conclusions at the end of the review. It should be noted that the terms "lotion" and "solution" are used interchangeably by the sponsor, and both refer to the product which is proposed for marketing. Also, "CD271" is the sponsor's code for adapalene.

A. Dermatotoxicity Studies:

1. Study Title: Skin Irritation Test in Healthy Volunteers Following Repeated Applications (21 Days) of Lotion CF 271/008 Containing Four Different Concentrations of CD271 (adapalene) (0.01%, 0.03%, 0.1% and 0.3%) - Study Report PC 85013/2.

Investigator: M. Verschoore, M.D.
Galderma
Nice, France

Method: This was intended to be a test of four concentrations of adapalene solution (0.01%, 0.03%, 0.1% and 0.3%) vs. the vehicle and the patch alone. However, the 0.3% strength precipitated during the test and so the results for the three lower strengths only were reported.

Twenty-four healthy adults were tested (6 male, 18 female, aged 19-52 years). Approximately 100 microliters of each substance were applied once daily, 6 days per week, for 3 weeks to test sites on the forearm and held in place with occlusive dressings. The patches were left in place 24 hours (48 hours on weekends) and then replaced with fresh test materials. Two subjects did not complete the study for reasons not related to drug application. Reactions were scored 30 minutes after patch removal (before the next patch was applied). All test applications and observations were double-blind. Scoring was

done on a scale from 0 = no reaction to 4 = intense erythema, edema, etc.

The protocol also included measurement of trans-epidermal water loss (TEWL) at each patch change.

Results: No patients demonstrated any edema during the test. Very little erythema was noted with either the patch alone or the vehicle plus patch. There were no scores above 1 for any test subjects. However, by the 22nd day 13 of 22 patients exhibited a 1 score to the 0.1% product (59%) vs. 7/22 for the 0.03% strength (32%) and 5/22 for the 0.01% strength (22%).

Comment: This study is inadequate to establish the irritancy potential of 0.1% adapalene solution. While the irritancy seen with all test preparations was mild, the 0.1% product was more irritating than the other products tested.

In order to properly test the irritancy potential of 0.1% adapalene, a similar study run in 100 patients, testing the finished dosage form, vehicle, and a reference product of known low irritancy (e.g. petrolatum) would be desirable. However, the following study may substitute for this protocol.

2. Study Title: Sensitization Test of Various Concentrations of CD 271 (adapalene) - Study Report PC 87031.

Investigator: M. Verschoore, M.D.
Galderma
Nice, France

Method: This was a test of the sensitization potential of adapalene solution 0.1% and 0.03% as well as the same strengths in two different gel vehicles (aqueous and alcoholic). The three vehicles alone were also tested.

105 healthy adults (53 males, 52 female, aged 19-48) were entered into the study. Five subjects failed to finish the study for reasons not related to drug application. 50 microliters of each test article was applied to predetermined test sites on the back and covered with occlusive tape for 48 hours. At the end of the 48 hour period, a 15 minute rest period was given, followed by observation for irritation. This procedure was repeated 3 times weekly for 3 weeks (induction phase). The test observer was blinded to the identity of the test material at each location. After a 2 week rest period, an unspecified amount of each formulation was applied at new test sites on the back for 48 hours under occlusion. Reactions were scored 24, 48, and 72 hours later on a scale from 0 = no reaction to 4 = red erythema, induration, vesicles, etc. (challenge phase).

Results: The results are presented for the 0.1% lotion, lotion vehicle, 0.1% gels and the two gel vehicles only. The following table represents the cumulative irritancy scores and cumulative sensitization scores for all readings (that is, the numbers represent the total scores seen for each product during the test periods for all 100 test patients).

Test Material	Induction	Challenge
Lotion vehicle	13	1.5
0.1% lotion	42	2.5
Gel vehicle "A"	72.5	8.5
0.1% gel "A"	93.5	4
Gel vehicle "B"	119	51
0.1% gel "B"	879	136.5

Comment: This study establishes that 0.1% adapalene lotion is not a sensitizer when tested by a standard protocol. Further, although the induction phase of the study was not performed according to standard irritation protocols (the patches are changed more often in an irritation study), the data does indicate that the lotion is not likely to be an irritant when tested by the standard protocol. Another irritation study is not necessary.

3. Study Title: Assessment of the Phototoxicity of Antiacne Lotion CF 271/008 (adapalene, 0.1%) and of its vehicle CF 008 - Study Report PH 87035.

Investigator: L. Duteil, Ph.D.
Hopital Pasteur
Nice, France

Method: This was a test of the phototoxicity potential of 0.1% and 0.03% adapalene solution and the solution vehicle in 13 healthy adults (8 male, 5 female, aged 20-31 years). 50 microliters of each test material was applied to the lumbar area of the spine (there was also an untreated control site). The sites were then irradiated with a UVA dose of 20 Joules/cm^2. There were identical test sites on the other side of the spine which were treated with test products and patched, but not irradiated. The sites were examined 1, 24, 48, and 72 hours post-irradiation for signs of skin toxicity on a scale from 0 = no reaction to 4 = erythema, induration, vesicles, etc. The test was run in double-blind fashion.

Results: No phototoxicity reactions were observed at any test sites.

Comment: This study provides adequate evidence that adapalene solution 0.1% possesses little potential to cause phototoxicity reactions.

4. Study Title: Assessment of the Photoallergic Contact Sensitization Potential of CF 271/008 (adapalene, 0.1%) and of its vehicle CF 008 - Study Report PH 87034

Investigator: L. Duteil, Ph.D.
Hopital Pasteur
Nice, France

Method: This was a test of the photoallergic potential of 0.1% and 0.03% adapalene solution and the solution vehicle in 28 healthy adults (19 male, 9 female, aged 19-38 years). This test consists of 3 phases: pre-test, induction and challenge. In the pre-test phase, the MED (Minimum Erythemal Dose) of each patient is determined using a solar simulator.

The study was run in double-blind fashion. In the induction phase, 50 microliters of each test article was applied twice weekly to test areas on the lumbar area of the back. The test sites were occluded for 24 hours, the patches removed, and the sites exposed to 3 MED's of radiation. The sites were left open for 48 hours (or 72 hours over a weekend). This cycle was repeated twice weekly for 3 weeks.

Two weeks later, the subjects returned for challenge. The test drugs were applied to new duplicate test sites. The sites were occluded for 24 hours, and one set of the duplicate patches was then uncovered. The uncovered sites were irradiated with 4 Joules/cm^2 of UVA. The covered test sites were then uncovered and the test sites evaluated 24, 48 and 72 hours after irradiation for signs of photoallergy on a scale from 0= none to 4 = severe.

Results: Most of the test subjects noted scores of 2 at all test sites (including vehicle) during the induction phase. This was probably due to irradiation with 3 MED's of UVB. There were no reactions at all seen during the challenge phase.

Comment: This study provides adequate evidence that adapalene solution 0.1% possesses little potential to cause photocontact allergenicity reactions.

5. Study Title: 21-Day Repeated Application Skin Irritation Testing of 0.1% CD 271 (adapalene) Solution Applied in Combination with Other Topical Anti-Acne Products - Study Report CR 91108.

Investigator: C. Raybaut, M.D.

Hopital Pasteur
Nice, France

Method: This was a test of 0.1% adapalene solution vs. other topical acne medications both alone and in combination. The other products tested were Cutacnyl 10 Gel (10% benzoyl peroxide), manufactured by Galderma in France; Eryfluid Solution (4% erythromycin), manufactured by in and manufactured by

Twenty-five healthy adults were tested (7 male, 18 female, aged 20-47 years). Approximately 20 microliters of the test products were applied to seven test sites on the upper back once daily 5 times per week for 3 weeks. The four test sites which received single ingredients only had the applications made either in the morning or evening. The three test sites whch combined 0.1% adapalene with one of the other test materials received adapalene in the evening and the other material in the morning.

No occlusion of the test materials was done. Assessment of irritation was made in the morning, before test material application, on a scale from 0 = no erythema to 4 = severe erythema, edema, etc.

Results: The following test groups displayed no irritation at all: Dalacine T, Eryfluid and Eryfluid plus adapalene 0.1%. The following test groups displayed minimal irritation (one or two patients had low readings on one or two days of the test): adapalene 0.1%, Dalacine T plus adapalene 0.1%, Cutacnyl 10. The only test group which displayed any significant irritation was the adapalene 0.1% plus Cutacnyl 10 (benzoyl peroxide) group. By the last day of the study, 10 of the 25 patients had irritation scores of 0.5 or 1.0.

Comment: This study is a hybrid which fails to establish (1) the irritancy potential of the various products and combinations, (because occlusion was not used on the test sites, which is standard procedure for irritancy determinations); or (2), that it is safe to use the products in combination clinically, because acne products are used longer than the 3 week length of this study, and they are used on diseased, not normal skin.

6. Study Title: Investigation of the Pharmacokinetic and Metabolic Profile of CD 271 (adapalene) Following a Single Topical Application of ^{14}C-CD271 in a Lotion in Human Volunteers - Study Report CIR/271/98001.

Investigator:

Method: This was a study of percutaneous absorption in 4 healthy males, aged 21-25. 0.5 mL of a solution containing 0.1% of ^{14}C labled adapalene was applied to their upper backs and left for 24 hours, protected by a non-occlusive gauze dressing. Blood samples were collected after 24 hours, and urines and feces were collected for 14 days. Tape stripping was performed at the application site in an attempt to evaluate the amount of drug in the stratum corneum.

Results: Very small amounts were recovered from the plasma of the test subjects (one subject had no plasma levels). One subject's adapalene levels ranged from ng/mL from hour 12 through hour 72 after application. A second subject had a level of 0.2 ng/mL at hour 12 and 0.1 ng/mL at hour 24. The third subject had only one reading : 0.036 ng/mL at hour 96.

Virtually no drug was recovered in the urine and total amounts excreted in the feces varied from 0.02% - 0.06% of the total dose administered.

The amounts of drug recovered from the surface varied from 98.9% to 89.4%.

Comment: This study will also be reviewed by our Biopharmaceutics staff, and the comments delivered here should be regarded as preliminary. Since the amount of radioactivity unaccounted for ranged from roughly 1% to 10% of the applied dose, it is difficult to draw any firm conclusions from the results of the study. Assuming the study was competently conducted, adapalene does not appear to be well absorbed through normal healthy skin.

B. Vehicle controlled Studies

The sponsor has identified 3 of the 6 submitted vehicle controlled studies as "pivotal". These include all three parallel group studies. The three small bilateral paired comparison studies will be reviewed first, followed by the three pivotal parallel group studies.

1. Study Title: Clinical Study of the Efficacy of CD271 Lotion 0.1% Applied to Limited Areas in the Treatment of Polymorphous Juvenile Acne - Study Report PC 86019.

Investigator: J. Thivolet, M.D.
Hopital Eduard Herriot
Lyon, France

Method:

a. **Study design:** This was a single-center, observer-blinded bilateral paired comparison study comparing the effectiveness and safety of Adapalene Solution 0.1% and its vehicle.

b. **Patient selection:** Male patients suffering from dorsal papulo-pustular acne vulgaris, with or without nodules or cysts, were chosen, who had not used any topical anti-acne medication on his back for at least a month.

c. **Patient exclusions:** These were patients with exclusively comedonal acne, acne fulminans or acne conglobata; patients who had used retinoic acid on their acne in the previous year; and patients who had taken an antibiotic in the previous month.

d. **Dosage and duration of treatment:** Two 10x10 cm areas were outlined on either side of the spine and treated with either the active or vehicle preparation by a technician twice daily. Therapy continued for 4 weeks, with evaluations done at 1, 2 and 4 weeks.

e. **Effectiveness parameters:** The clinical observer counted lesions (comedones, papules, pustules, cysts) in each treatment area and recorded an overall clinical evaluation on a scale from 0 (complete clearing) to 10 (worst acne) at each visit.

f. **Safety evaluation:** The patients were examined for erythema, dry skin, pruritus and burning at each visit, and the reactions graded on a scale from 0 = none to 3 = maximum.

Results:

a. **Evaluable patients:** Eleven patients entered the study. Two of these left the study early because of adverse reactions (see the safety summary below). The other 9 patients completed the 4 week treatment period.

b. **Demographics:** All patients were males, aged 18-30 years (mean = 24.5 years). Other demographic data are not given, except that previous duration of disease was 18-150 months.

c. **Effectiveness:**

i. Lesion counts: The sponsor has presented only percentage reductions in lesion counts in the 9 patients who completed the study, as follows:

	% Reduction	
Lesion Types	Adapalene	Vehicle
Closed comedones	16.5%	9.1%
Open comedones	33.8%	1.3%

Non-inflammatory lesions	37.0%	7.8%
Inflammatory lesions (papules, pustules)	54.9%	29.4%

ii. Global evaluation: No summary of the results is presented by the sponsor. The raw data indicate that most patients' global evaluation did not change during the 4 week treatment period.

d. **Safety:** One patient left the study after 3 weeks because of an "important" irritant reaction to the active product (not graded). Another patient left the study before the last evaluation because of a reaction to the active product (erythema = 1, pruritus = 2, burning = 3).

Five subjects had adverse reactions to the active product and no reaction to the vehicle. Two patients had reactions to both active and vehicle. Reactions in the active group included erythema in 5 subjects, pruritus (5), burning (4) and dry skin (1) (some subjects had more than one reaction). The adverse events in the vehicle group were one each of burning and pruritus.

Comment: Since this study is so small, no critical analysis of the efficacy data was attempted. The sponsor does not contend that efficacy is demonstrated. This study does indicate that the active product was considerably more irritating than the vehicle. Two of eleven patients left the study early because of adverse events related to the active product.

2. Study Title: Clinical Study of the Safety and Efficacy of a Lotion Containing 0.1% CD 271 Used in the Treatment of Acne - Study Report PH 86013.

Investigator: L. Juhlin, M.D.
University Hospital
Uppsala, Sweden

Method:

a. **Study design:** This was a single-center double-blind bilateral paired comparison study comparing the effectiveness and safety of Adapalene Solution 0.1% and its vehicle.

b. **Patient selection:** Patients of either sex with "polymorphous" juvenile acne of the face, who had not used any topical anti-acne medication for at least a month, or Accutane for at least 6 months.

c. **Patient exclusions:** These were patients with exclusively comedonal acne, acne fulminans or acne conglobata.

d. **Dosage and duration of treatment:** This was an out-patient study in which the patient made applications of the test products to the left or right side of the face from drug containers coded "left" or " right". Ten drops of the proper product was applied to one side of the face twice daily for 8 weeks. There were examinations at weeks 1, 2, 4 and 8.

e. **Effectiveness parameters:** The clinical observer counted lesions (comedones, macules, papules, pustules, cysts) on each side of the face and recorded an overall clinical evaluation on a scale from 0 (complete clearing) to 10 (worst acne) at each visit.

f. **Safety evaluation:** The patients were examined for erythema, dry skin, pruritus and burning at each visit, and the reactions graded on a scale from 0 = none to 3 = maximum.

Results:

a. **Evaluable patients:** Ten patients entered and completed the study.

b. **Demographics:** There were 9 male patients and 1 female patient. Their ages ranged from 17-20 years. No other deomographic information is available.

c. **Effectiveness:**

i. Lesion counts: The sponsor has presented percentage reductions in lesion counts as follows:

	% Reduction	
Lesion Type	Adapalene	Vehicle
Non-inflammatory	71%	38%
Inflammatory	82%	55%
Total Lesions	75%	68%

ii. Global evaluation: Again, no summary of these results are presented. The raw data indicate that most global evaluation grades were unchanged or one digit lower (e.g.,7 to 6) at the end of the study.

d. **Safety:** Five subjects had adverse reactions to the active product but none to the vehicle. One subject had no adverse reactions to either preparation. Reactions in the active group included dryness in 9 subjects, erythema (6), pruritus (2) and burning (3) (some subjects had more than one reaction). In the vehicle group, the reactions were dryness (4), erythema (4), and pruritus (1).

Comment: Again, no critical analysis has been performed on the efficacy data since the study is so small and the sponsor does not claim that the study demonstrates superiority of active over

vehicle. There were approximately twice as many adverse reactions in the active group than in the vehicle group.

3. Study Title: Clinical Study of the Safety and Efficacy of CD 271 Lotion 0.1% in the treatment of Acne - Study Report PC 86012

Investigator: L. Juhlin, M.D.
University Hospital
Uppsala, Sweden

Method:

a. **Study design:** This was a single-center observer-blinded bilateral paired comparison study comparing the effectiveness and safety of Adapalene Solution 0.1% and its vehicle.

b. **Patient selection:** Male patients suffering from dorsal "polymorphous" juvenile acne were chosen who had not used any topical anti-acne medication on his back for at least a month, or had taken Accutane for at least 6 months.

c. **Patient exclusions:** These were patients with exclusively comedonal acne, acne fulminans or acne conglobata.

d. **Dosage and duration of treatment:** Two 10 x 10 cm areas were outlined on either side of the spine and treated with 10 drops of either the active or vehicle preparation by a technician twice daily. Therapy continued for 8 weeks, with evaluations done at 1,2, 4 and 8 weeks.

e. **Effectiveness parameters:** The clinical observer counted lesions (comedones, macules, papules, pustules, nodules and cysts) in each treatment area and recorded an overall clinical evaluation on a scale from 0 (complete clearing) to 10 (worst acne) at each visit.

f. **Safety evaluation:** The patients were examined for erythema, dry skin, pruritus and burning at each visit, and the reactions graded on a scale from 0 = none to 3 = severe.

Results:

a. **Evaluable patients:** Ten patients entered and completed the study.

b. **Demographics:** All patients were male, aged 17-23 (mean = 19.6 years). No other demographic information is available.

c. **Effectiveness:** The sponsor has not presented any summary data except to state that there was no significant difference in

lesion reduction between the treatment groups. The sponsor theorizes that initial lesion counts were too low to demonstrate differences.

d. **Safety:** One patient experienced a vesiculobullous reaction on the adapalene side on day 28 which subsided when treatment was reduced to once daily, rather than twice daily. There were no adverse reactions reported for the vehicle group. For the adapalene group, the total numbers of reactions were dry skin (7), pruritus (7), erythema (6) and burning (5) (some subjects exhibited more than one reaction).

Comment: No independent evaluation of the efficacy data was done. This study indicates that the active product caused many more adverse reactions than did the vehicle. This corroborates the results seen in study 1 above, and raises the question of whether adapalene solution is suitable for use in acne on the back. Three of 21 patients (14%) who were treated for acne of the back with adapalene in this study and in study 1. above exhibited relatively severe adverse effects after using the drug for a month or less.

4. (pivotal) Study Title: Controlled Safety and Efficacy Study of CD271 Lotion 0.1% vs Vehicle in the Treatment of Acne - Study Report PC 86030

Investigator: S. Jablonska, M.D.
Warsaw School of Medicine
Warsaw, Poland

Method:

a. **Study design:** This was a single-center, double-blind, randomized, parallel group study comparing the effectiveness and safety of Adapalene Solution 0.1% and the solution vehicle.

b. **Patient selection:** Male patients of at least 15 years of age with a diagnosis of acne vulgaris who had total lesion counts of at least 20 (presumably on the face, since this area only was studied) and at least 10 inflammatory lesions were selected.

c. **Patient exclusions:** These were patients with exclusively comedonal acne, acne fulminans or acne conglobata, as well as those who had used any topical anti-acne treatment in the last month or Accutane within the last 6 months.

d. **Dosage and duration of treatment:** The patients applied the medications themselves. They were instructed to place 10 drops

of the test product on a cotton pad twice daily and apply it to acne lesions as needed. Treatment continued for 8 weeks, with evaluations done at weeks 1, 2, 4 and 8.

e. **Effectiveness parameters:** The clinical observer counted lesions (comedones, macules, papules, pustules, nodules and cysts) at each treatment visit. The protocol also provides for a general assessment of acne by the investigator, although no scale for this assessment is given. In addition, the protocol provides for recording the "opinions" of the investigator and the patients concerning the therapy, but no scale is given.

f. **Safety evaluation:** The patients were examined for erythema, dry skin, pruritus and burning at each visit, and the reactions graded on a scale from 0 = none to 3 = severe. Blood samples were taken from 10 of the 15 active group patients at the end of the study and 1, 2 and 7 days later and analyzed for adapalene content.

Results:

a. **Evaluable patients:** Thirty subjects entered the study, 15 in each group. One patient in the vehicle group left the study because of an infection (pharyngeal abscess) not related to treatment.

b. **Demographics:** The patients were all male, aged 15-26 years. No other demographic information is available.

c. **Effectiveness:** Results are presented for the end of treatment (8 weeks).

i. Comedones (non-inflammatory lesions)

Mean comedone counts and % reduction

Treatment	Mean at Baseline (n)	Mean at 8 Weeks (n)
Adapalene	133 (15)	41 (15) (69%)
Vehicle	143 (15)	88 (14) (38%)

ii. Papules, pustules, nodules, cysts (inflammatory lesions)

Mean inflammatory lesion counts and % reduction

Treatment	Mean at Baseline (n)	Mean at 8 Weeks (n)
Adapalene	44 (15)	22 (15) (65%)
Vehicle	61 (15)	48 (14) (21%)

iii. Total lesions

Total lesion counts and % reduction

Treatment	Mean at Baseline (n)	Mean at 8 Weeks (n)
Adapalene	176 (15)	62 (15) (65%)
Vehicle	204 (15)	136 (14) (33%)

iv. Global assessment (physician and patient). No data is presented concerning these variables.

d. **Safety:** Most patients displayed at least one adverse event during the study (the majority of patients had more than one reaction). The following table relates the number of patients who had specific reactions for each treatment:

	Adapalene	Vehicle
Erythema	15 (100%)	6 (43%)
Dryness	15 (100%)	7 (50%)
Burning	14 (93%)	6 (43%)
Pruritus	12 (80%)	7 (50%)

There were also more intense reactions (grades 2 and 3) in the adapalene group.

No adapalene was detected in the plasma of the patients sampled (limit of method = 1 ng/mL)

Comment: This study may not be accepted as pivotal, primarily because there was no meaningful physician global evaluation, and only males were studied. While lesion counts are important, an overall impression of symptomatology (erythema, scaling, etc.) is necessary to confirm that the appearance of the patient has actually improved. It is expected that a pivotal study will include representatives of all patient groups the drug is intended to treat (including females, in this case). Further, there is an apparent imbalance in inflammatory lesions and total lesions at baseline. The vehicle group had 16% more total lesions and 39% more inflammatory lesions at study entrance.

All adapalene patients experienced some adverse events, and most adapalene patients experienced all reactions which were evaluated.

5. (pivotal) Study Title: Clinical Safety and Efficacy

Comparison of Topical CD 271 Lotion 0.1% with CD 271 Lotion Vehicle in Patients with Acne Vulgaris - Study Report C-88-27.

Investigators: E.L. Jones, M.D.
Hill Top Research, Inc.
Miamiville, OH

J.J. Kantor, M.D.
Research Testing Labs
Little Neck, N.Y.
Subinvestigators:
A. Simon, Ph.D.
I. Weinstock, Ph.D.

J.M. Swineheart, M.D.
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A.H. Greenspan, M.D.
TKL, Inc.
Maywood, N.J.
Subinvestigators:
M. Kahn, M.D.
R. Reardon, Ph.D.

Method:

a. **Study design:** This was a multicenter, randomized, double-blind, parallel-group comparison of the effectiveness and safety of Adapalene Lotion 0.1% and its vehicle.

b. **Patient selecion:** Patients of both sexes, aged 12-30 years, were enrolled. The patients were to have Grade 1 through 5 facial acne on the Cunliffe scale (this is equivalent to Grade 2 or 3 acne on the more commonly used 4 - point scale, and is generally defined as mild to moderate disease). All patients were to have had at least 10 inflammatory and 20 noninflammatory lesions on the face at study entrance. The female patients were required to use adequate birth control during and for one month after the study, and agree to have a pregnancy test before and during the study.

c. **Patient exclusions:** The following list of exclusions is taken directly from the sponsor's submission:

" 1. Patients with:

a. Less than Grade 1 and greater than Grade 5 acne vulgaris.

b. Less than 20 comedos and less than 10 inflammatory lesions.

c. Acne conglobata

d. Acne fulminans

e. Secondary acne (chlorine, drug induced acne, etc.)

f. Underlying diseases or other dermatological conditions that require the use of interfering topical or systemic therapy.

g. Known sensitivities to any of the study preparations.

h. Males with a mustache or beard.

i. Female patients taking birth control pills less than three months before study.

2. Patients who have received:

a. Topical acne treatment within the past two weeks.

b. Systemic antibiotics within the past 4 weeks (excluding penicillins).

c. Systemic retinoid treatment within the past six months.

d. Topical or systemic anti-inflammatory treatment within the past four weeks.

3. Female patients of child bearing potential will submit to a urine pregnancy test each visit. If pregnancy is determined the patient will be terminated from the study. Written, signed results will be sent to Alcon to be placed in the patient's study file."

d. **Dosage and duration of treatment:** Applications were to be made once daily to the face and other affected areas by the patients (this was an outpatient study) for 12 weeks.

e. **Effectiveness parameters:** The patients were evaluated at baseline and at 2, 4, 8 and 12 weeks.

i. Global evaluation: The patients' global response to treatment was assessed by comparing the condition of the patient to a series of representative photographs of acne patients based on the Cunliffe scale of 0 to 7, with 0 = no acne to 7 = most severe acne. The following represents the relationship between the commonly used four-point scale and the Cunliffe scale:

Four-point scale	Cunliffe scale
0	0
1	0.25,0.50,0.75
2	1,1.5,2
3	3,4,5
4	6,7

ii. Lesion counts: Inflammatory (papules and pustules) and non-inflammatory (open and closed comedones) lesions were the primary efficacy variable and were counted at each visit. Only facial lesions were counted, although the global evaluation also included the chest, back, etc. if these areas were involved. In order to facilitate counts, the face was divided into quadrants (forehead, cheeks, chin). Nodules and cysts were also counted, when present, and included in the inflammatory lesion counts.

iii. Protocol extension: All sites were given the option of continuing their patients on the active product for an additional 9 months at the end of the study. The primary purpose of this was to gather long term safety data.

f. **Safety evaluation:**

i. Patients were examined for adverse reactions during the course of the study.

ii. Erythema. oilness, dryness, scaling, pruritus and burning were evaluated on a scale from 0 = none to 3 = severe.

Results:

a. **Evaluable patients:** There were 110 patients, 55 per treatment, enrolled into the study. The following table represents the number of patients enrolled by investigator:

	No. Subjects Treated	
Investigator	Adapalene	Vehicle
Jones	15	15
Kantor	15	15
Swineheart	15	15
Greenspan	10	10
	55	55

The protocol required that patients be required to complete at

least 4 weeks of treatment to be evaluable for efficacy. Thirteen patients left the study prior to 4 weeks and were thus not evaluable for efficacy. Six were Adapalene patients and seven were vehicle patients. Thus, there was a total of 97 evaluable efficacy patients, 49 Adapalene and 48 vehicle. All patients were evaluable for safety.

There were 7 patients (3 in the Adapalene group and 4 in the vehicle group) who discontinued the study due to adverse reactions. Please see the safety evaluation below for more information on these patients.

There were seven additional patients (5 Adapalene, 2 vehicle) who did not complete the study, even though they were evaluable for efficacy. The following table presents the reasons for discontinuation by treatment group(these totals include the 13 who were not evaluable for efficacy and 7 who discontinued early, but were evaluable):

Reason for Discontinuance	Adapalene	Vehicle
Adverse event	3	4
Patient request	1	1
Interfering Therapy	0	1
Lost to follow-up	7	3
	11	9

Additionally, there were 13 patients (6 Adapalene, 7 vehicle) who were protocol violations. These included 1 Adapalene patient whose baseline noninflammatory lesion count was one (rather than the minimum 20). The other 12 protocol violators took oral antibiotics for 6 days or longer during the study.

In summary, it is not felt that the one lesion count violation in the Adapalene group is critical to the interpretation of the data. This patient remains in the data summaries. However, it should be stated that the patients still in the data summaries who are protocol violators by virtue of antibiotic ingestion may have displayed improvement in their acne due to oral antibiotic, rather than topical therapy. The sponsor was asked to reanalyze the data to exclude the antibiotic ingestion group. Please see the Addendum at the end of this review for the results of that analysis.

b. **Demographics:** The demographics for the efficacy evaluable patients are as follows:

Characteristics	Adapalene	Vehicle
No. of subjects	49	48
Sex Male	31	27
Female	18	21
Age (yr) -mean	19.5	19.2
Race		
White	47	46
Black	2	1
Other	0	1

c. **Effectiveness:** Results are presented at the end of 12 weeks. Because all patients did not report for every evaluation an "Endpoint" presentation is included. "Endpoint" is the last valid visit for all evaluable patients.

i. Physician global evauation. The data has been presented by the sponsor in both the traditional 4 point scale and the Cunliffe (7 point) scale. The 4 point scale will be used here. The data has been translated to the 4 point scale from the Cunliffe scale by the sponsor.

Global Grade - n and % of n

Week	Treatment	0	1	2	3	N
0	Adapalene	0	0	47(96%)	2(4%)	49
	Vehicle	0	0	43(92%)	4(8%)	48
12	Adapalene	0	31(71%)	13(29%)	0	44
	Vehicle	1(2%)	27(59%)	16(35%)	2(4%)	46
Endpoint	Adapalene	0	32(65%)	17(35%)	0	49
	Vehicle	1(2%)	27(57%)	17(36%)	2(4%)	48

ii. Non-inflammatory lesions (open and closed comedones)

Mean lesion counts and % reduction

Week	Treatment	Mean	N
0	Adapalene	53.6	49
	Vehicle	49.2	48
12	Adapalene	33.8(37%)	44
	Vehicle	31.9(35%)	46
Endpoint	Adapalene	35.9(33%)	49
	Vehicle	35.3(28%)	48

iii. Inflammatory lesions (papules, pustules, nodules, cysts)

Mean lesion counts and % reduction

Week	Treatment	Mean	N
0	Adapalene	25.3	49
	Vehicle	22.1	48
12	Adapalene	20.9(17%)	44
	Vehicle	19.3(13%)	46
Endpoint	Adapalene	23.7(6%)	49
	Vehicle	20.3(8%)	48

iv. Total lesions (inflammatory and non-inflammatory)

Mean lesion counts and % reduction

Week	Treatment	Mean	N
0	Adapalene	78.9	49
	Vehicle	71.3	48
12	Adapalene	54.7(31%)	44
	Vehicle	51.2(28%)	46
Endpoint	Adapalene	59.6(24%)	49
	Vehicle	55.6(22%)	48

v. Protocol extension: Only 17 patients elected to continue to use the active medication after the 12-week study period ended. There were 10 patients from the Adapalene group and 7 from the vehicle group. No efficacy data is presented for these patients.

d. **Safety:**

i. Adverse reactions: There were 7 patients (3 in the Adapalene group and 4 in the vehicle group) who discontinued the study due to adverse reactions. The reasons in the Adapalene group were erythema, skin discomfort and pruritus. In the vehicle group, they were pruritus, skin discomfort, skin irritation and a case of otitis media in one patient which was probably not related to therapy. The following table presents the adverse reactions which were probably or possibly related to drug therapy.

Number and % of adverse reactions

Event	Adapalene (N = 55) N	%	Vehicle (N = 55) N	%
Erythema	5	(9.0)	0	
Discomfort Skin	5	(9.0)	2	(3.6)
Pruritus	3	(5.4)	2	(3.6)
Dry Skin	1	(1.8)	0	
Irritation Skin	0		1	(1.8)
Dermatitis	1	(1.8)	0	
Excoriation	0		1	(1.8)
Total	15	(27)	6	(11)

ii. Erythema, oiliness, dryness, scaling, pruritus, burning: The percentages of patients in each group who experienced increased, decreased, and unchanged evaluations of each of these phenomena at the end of 12 weeks, as compared to baseline will be presented.

% of Patients at 12 weeks				
Reaction	Treatment	Decreased	Same	Increased
Erythema	adapalene	11%	52%	36%
	vehicle	26%	60%	15%
Oiliness	adapalene	48%	41%	11%
	vehicle	51%	38%	11%
Dryness	adapalene	0	64%	36%
	vehicle	11%	62%	28%
Scaling	adapalene	0	75%	25%
	vehicle	6%	75%	19%
Burning	adapalene	2%	86%	11%
	vehicle	2%	92%	6%
Pruritus	adapalene	7%	66%	27%
	vehicle	2%	87%	11%

Comment: This study fails to demonstrate the superiority of Adapalene Solution 0.1% over its vehicle. By the sponsor's own statistical analysis, none of the efficacy variables evaluated demonstrated superiority of active over vehicle at p = 0.05 or less. The sponsor states that about 20% of the Adapalene patients achieved at least a 75% reduction in total lesion counts as compared to about 5% of the vehicle patients. Thus, one could make the case that for a select group of patients studied (about 15%), Adapalene provides a great benefit, although if the other side of this statistic is considered, it appears that the majority of patients did as well (or better) on vehicle than the active product. No separate analysis of these patients was

provided by the sponsor.

In any event, the standard for approval of acne products in this Division is that the mean lesion count reduction must be statistically superior in the active group over the total patient populace, not a small subgroup. It would be necessary to do further research to properly identify the subgroup most likely to be helped if this were to be used as a basis for approving the product. Otherwise, the great majority of patients would receive no benefit from the product.

The FDA statistical review finds no difference between the groups in physician global evaluation. She agrees with the sponsor's lesion count analysis by subgroup.

About 27% of the Adapalene patients experienced adverse reactions in the study, as opposed to 11% of the vehicle patients. Further, when six separate signs and symptoms were separately evaluated, the Adapalene patients experienced significantly increased erythema and pruritus as compared to vehicle at the end of the study.

6. (pivotal) Study Title: Clinical Safety and Efficacy Evaluation of 0.1% CD 271 Lotion vs. CD 271 Lotion Vehicle - Study Report 9104-CD271L-EV

Investigator: E. Ast, M.D.
Research Testing Labs., Inc.
Huntington Station, N.Y.

S.I. Cullen, M.D.
Gainesville, FL

F.E. Dunlap, M.D.
Argus Research, Inc.
Tucson, AZ

B. Potter, M.D.
Georgia Clinical Research Center, Inc.
Atlanta, GA

J. Hickman, M.D.
The Education and Research Foundation
Lynchburg, VA

A.W. Lucky, M.D.
Dermatology Research Associates, Inc.
Cincinnati, OH

M. Rappaport, M.D.
Calabasas, CA

R. Stoughton, M.D.
UC - San Diego
La Jolla, CA

Method:

a. **Study Design:** This was a multi-center, randomized, double-blind, parallel-group comparison of the effectiveness and safety of Adapalene Lotion 0.1% and its vehicle.

b. **Patient Selection:** Patients of both sexes, aged 12-30 years, were enrolled. The patients were to have Grade 1 through 5 facial acne on the Cunliffe scale (this is equivalent to Grade 2 through 4 acne on the more commonly used 4 point scale, and is generally defined as mild to moderate disease). All patients were to have had at least 10 inflammatory and 30 noninflammatory lesions on the face at study entrance. The female patients were required to use adequate birth control during and for 3 months after the study, and agree to have a pregnancy test before and during the study.

c. **Patient exclusions:** The following list of exclusions is taken directly from the sponsor's submission:

"Patient:

i) had acne conglobata

ii) had acne fulminans

iii) had secondary acne (chloracne, drug-induced acne, etc.)

iv) had underlying disease or another dermatological condition that required the use of interfering topical or systemic therapy

v) had known sensitivity to any of the study preparations

vi) had a beard

vii) had started taking birth control pills less than 3 months prior to entering the study or had discontinued birth control pills less than 6 months prior to entering the study (female patients of childbearing potential)

viii) was pregnant or lactating

ix) refused to discontinue from sunbathing during the study period."

d. **Dosage and duration of treatment:** Applications were to be made once daily to the face and other affected areas by the patients (this was an outpatient study) for 12 weeks. The protocol permitted a switch to every other day dosing if irritation became a problem.

e. **Effectiveness parameters and Safety parameters:** The effectiveness and safety parameters were the same as for study 5 above, except there was no provision in the protocol for additional treatment at the end of the blinded portion of the study.

Results:

a. **Evaluable patients:** There were 243 patients enrolled in the study (121 adapalene, 122 vehicle). All patients were evaluable for safety.

All patients who completed 4 weeks of therapy were considered to be evaluable for efficacy. The following table presents the number of patients per investigator who enrolled in the study, as well as the number of patients who completed the entire 12 week study and the number of patients evaluable for efficacy (had at least 4 weeks of therapy).

Investigator	Treatment Group	Patients Entering Study	Patients Discontinuing Early	Patients Completing Study	Patients Evaluable for Efficacy
Ast	CD-271L	10	0	10	10
	Vehicle	10	1	9	9
Cullen	CD-271L	10	2	8	9
	Vehicle	10	3	7	8
Dunlap	CD-271L	19	6	13	17
	Vehicle	19	3	16	19
Hickman	CD-271L	21	6	15	13
	Vehicle	21	1	20	20
Lucky	CD-271L	18	3	15	17
	Vehicle	17	2	15	15
Potter	CD-271L	15	2	13	14
	Vehicle	15	2	13	14
Rapaport	CD-271L	16	2	14	14
	Vehicle	15	1	14	14
Stoughton	CD-271L	12	2	10	10
	Vehicle	15	1	14	14
Treatment Totals	CD-271L	121	23	98	104
	Vehicle	122	14	108	113

The table presents the reasons for discontinuation by treatment group:

Reason for Discontinuance	Adapalene	Vehicle
Adverse Event	8	5
Patient Request	8	4
Lost to Follow-up	6	1
Non-compliant	1	4
Totals	23	14

The patients who discontinued due to adverse events will be discussed in the safety evaluation below.

There were 5 patients (3 Adapalene, 2 vehicle) who were protocol violations because they had fewer than 30 noninflammatory lesions at baseline and two patients who used conflicting oral antibiotics (one in each group).

These patients have been excluded from the efficacy data. There were 3 additional Adapalene patients and 7 additional vehicle patients who used antibiotics but who were not excluded from the efficacy analysis (see the Addendum at the end of this review for analysis of these patients).

b. **Demographics:** The demographics for the safety evaluable patients (all patients entering the study) as are follows:

Characteristics	Adapalene	Vehicle
No. of Subjects	121	122
Sex		
Male	69 (57%)	62 (51%)
Female	52 (43%)	60 (49%)
Age (yr) - mean	17.8	18.4
Race		
White	97 (81%)	100 (82%)
Black	13 (11%)	16 (13%)
Oriental	5 (4%)	4 (3%)
Other	6 (5%)	2 (2%)

c. **Effectiveness:** Results are presented at the end of 12 weeks. Because all patients did not report for every evaluation, an "Endpoint" presentation is included. "Endpoint" is the last valid visit for all evaluable patients.

The reviewers have checked the line listings and are in agreement with the sponsor's representation of the data.

i. Physician global evaluation. The sponsor states that Dr. Rappaport had "discrepancies" in his method of global assessment, and so they have deleted his data from the summarized global evaluations. Apparently Dr. Rappaport did not use the Cunliffe scale in performing this evaluation.

The data has been transformed from the Cunliffe scores to the 4 point scale score.

Global Grade - n - and % of n						
Week	Treatment	0	1	2	3	N
0	Adapalene	0	0	84 (93%)	6 (7%)	90
	Vehicle	0	0	91 (92%)	8 (8%)	99
12	Adapalene	0	36 (44%)	45 (56%)	0	81
	Vehicle	0	24 (26%)	62 (68%)	5 (6%)	91
Endpoint	Adapalene	0	40 (45%)	47 (53%)	1 (1%)	88
	Vehicle	0	24 (25%)	67 (69%)	6 (6%)	97

ii. Non-inflammatory lesions (open and closed comedones)

Mean lesion counts and % reduction			
Week	Treatment	Mean	N
0	Adapalene	61.5	104
	Vehicle	65.3	113
12	Adapalene	38.7 (37%)	95
	Vehicle	55.5 (15%)	105
Endpoint	Adapalene	40.3 (34%)	102
	Vehicle	57.6 (12%)	112

It is noted in this and the following tables that the endpoint patient totals are not the same as the evaluable patient totals. This is because 2 adapalene patients and one vehicle patient had endpoint visits which were "unevaluable", according to the sponsor. In addition, 3 patients in each group did not have lesion counts at week 12. It is not felt that these missing patients will affect the statistical outcomes of the study.

iii. Inflammatory lesions (papules and pustules)

Mean lesion counts and % reduction			
Week	Treatment	Mean	N
0	Adapalene	18.0	104
	Vehicle	19.5	113
12	Adapalene	12.8 (29%)	95
	Vehicle	14.0 (29%)	105
Endpoint	Adapalene	12.9 (28%)	102
	Vehicle	14.1 (28%)	112

iv. Total lesions (inflammatory and non-inflammatory)

Mean lesion counts and % reduction			
Week	Treatment	Mean	N
0	Adapalene	79.[illegible]	104
	Vehicle	84.8	113
12	Adapalene	51.5 (35%)	95
	Vehicle	69.5 (18%)	105
Endpoint	Adapalene	53.2 (33%)	102
	Vehicle	71.7 (15%)	112

Efficacy Comment: By the sponsor's statistical analysis, the active product was statistically significantly superior to vehicle in reduction in total lesions ($p = 0.017$) and noninflammatory lesions ($p = 0.005$) at week 12, and superior in global evaluation ($p = 0.003$). There was no significant difference in inflammatory lesion reductions.

There is a difficulty with the results in that there is apparently significant treatment x investigator interaction by the sponsor's analysis. This is best appreciated by the following presentation of mean total lesion counts by investigator.

Mean total lesion counts and % reduction				
Investigator	Baseline	N	Week 12	N
Ast				
Adapalene	56	10	57 (+2%)	10
Vehicle	99	9	72 (-27%)	9
Cullen				
Adapalene	83	9	36 (-57%)	8
Vehicle	84	8	61(-27%)	7
Dunlap				
Adapalene	97	17	56 (-42%)	14
Vehicle	108	18	81 (-25%)	16
Hickman				
Adapalene	73	13	77 (+6%)	12
Vehicle	82	20	114 (+39%)	19
Lucky				
Adapalene	101	17	60 (-41%)	16
Vehicle	100	15	83 (-17%)	15
Potter				
Adapalene	75	14	56 (-25%)	11
Vehicle	74	14	51 (-31%)	12
Rapaport				
Adapalene	73	13	23 (-69%)	14
Vehicle	77	14	30 (-61%)	13
Stoughton				
Adapalene	56	10	43 (-23%)	10
Vehicle	52	14	36 (-31%)	14

The sponsor's analysis indicates that the treatment x investigator significance is caused by Dr. Hickman and/or Dr. Ast. Dr. Hickman's patients experienced net increases in lesions for both treatment groups. She also lost a relatively high number of patients in the active group (only 13/21 were evaluable). Dr. Ast found the vehicle to be more effective than the active product.

Thus, of 8 investigators, there is one apparent outlier in terms of patient response (Dr. Hickman); one who found the vehicle to be much better than the active (Dr. Ast); three who found the active and vehicle to be roughly equivalent (Drs. Potter, Rapaport, Stoughton); and three who found the active product to

be much better than the vehicle (Drs. Cullen, Dunlap, Lucky). It is also noteworthy that Dr. Ast had a much higher baseline lesion count in the vehicle group than in the active group, which would have given his vehicle group more room to improve.

The sponsor was asked by the reviewers to reanalyze the data to remove (a) Dr. Hickman, (b) Dr. Ast and (c) both investigators from the data base. The sponsor submitted this information in an amendment dated September 17, 1993. The following tables compare the data with all 8 investigators, 7 investigators (without Hickman), 7 investigators (without Ast) and 6 investigators (without Hickman or Ast)

i. Non-inflammatory lesions (open and closed comedones)

Mean lesion counts and % reduction					
Week	Treatment	Original Mean	Mean less Hickman	Mean less Ast	Mean less Hickman & Ast
0	Adapalene	61.5	61.7	63.4	64.0
	Vehicle	65.3	65.4	64.0	63.8
12	Adapalene	38.7 (37%)	34.6 (44%)	37.9 (40%)	33.1 (48%)
	Vehicle	55.5 (15%)	45.2 (31%)	55.6 (13%)	44.1 (31%)
Endpoint	Adapalene	40.3 (34%)	37.0 (40%)	39.8 (37%)	35.9 (44%)
	Vehicle	57.6 (12%)	48.5 (26%)	57.9 (10%)	47.8 (25%)

ii. Inflammatory lesions (papules and pustules)

Mean lesion counts and % reduction					
Week	Treatment	Original Mean	Mean less Hickman	Mean less Ast	Mean less Hickman + Ast
0	Adapalene	18.0	18.7	18.6	19.4
	Vehicle	19.5	20.0	19.6	20.2
12	Adapalene	12.8 (29%)	13.2 (29%)	13.0 (30%)	13.5 (30%)
	Vehicle	14.0 (29%)	14.5 (27%)	13.6 (27%)	14.1 (30%)
Endpoint	Adapalene	12.9 (28%)	13.4 (28%)	13.1 (30%)	13.7 (29%)
	Vehicle	14.1 (28%)	14.8 (26%)	13.8 (30%)	14.5 (28%)

iii. Total lesions (inflammatory and non-inflammatory)

Mean lesion counts and % reduction					
Week	Treatment	Original Mean	Mean less Hickman	Mean less Ast	Mean less Hickman + Ast
0	Adapalene	79.5	80.4	82.0	83.4
	Vehicle	84.8	85.4	83.6	84.0
12	Adapalene	51.5 (35%)	47.9 (40%)	50.9 (38%)	46.6 (44%)
	Vehicle	69.5 (18%)	59.7 (30%)	69.2 (17%)	58.2 (31%)
Endpoint	Adapalene	53.2 (33%)	50.4 (37%)	52.9 (36%)	49.6 (41%)
	Vehicle	71.7 (15%)	63.3 (26%)	71.7 (14%)	62.3 (26%)

iv. Physician global evaluation

The mean global grades will be given to facilitate comparison.

Mean global grade and % reduction					
Week	Treatment	Original Mean	Mean less Hickman	Mean less Ast	Mean less Ast + Hickman
0	Adapalene	1.51	1.52	1.56	1.58
	Vehicle	1.54	1.52	1.55	1.53
12	Adapalene	1.00 (33%)	0.94 (38%)	1.01 (35%)	0.95 (40%)
	Vehicle	1.24 (19%)	1.21 (20%)	1.25 (19%)	1.21 (21%)
Endpoint	Adapalene	1.01 (33%)	0.97 (36%)	1.03 (34%)	0.98 (36%)
	Vehicle	1.27 (18%)	1.25 (18%)	1.28 (17%)	1.25 (18%)

Some comments are appropriate concerning the analysis:

a. Even though Dr. Ast found the vehicle to be more effective than the active and his vehicle patients had more lesions than his active patients, his total number of patients was so small that his removal from the data does not greatly influence the results. It should be noted that the sponsor states in this amendment that their new analysis indicates that only Dr. Ast creates significant treatment by investigator interaction in the data (that is, their position now is that Dr. Hickman should remain in the analysis).

b. Removal of either Hickman or Ast or both does not significantly affect the inflammatory lesion data or mean global grade data.

c. Removal of Dr. Hickman from the data does influence non-inflammatory lesion count and total lesion count results. The following table shows the changes in p-value calculated by the sponsor at 12 weeks and endpoint for non-inflammatory lesions and total lesions:

p-value, active vs. vehicle				
	Week 12		Endpoint	
Parameter	All Investigators	Less Hickman	All Investigators	Less Hickman
Total lesions	0.02	0.04	0.03	0.09
Non-inflammatory Lesions	0.005	0.01	0.009	0.03

Thus, if the sponsor's analysis is accepted, and Dr. Hickman is left in the data, the active is superior to vehicle at both time points for both variables. If Dr. Hickman is removed from the data, the active is no longer superior to vehicle in total lesions at endpoint.

Despite the above comments, the sponsor appears to have established the superiority of active to vehicle in mild to moderate facial acne with this study. This conclusion is supported by the review of FDA's statisticians. They find that (see addendum by Dr. Srinivasan) there is no reason to drop any of the investigators from the analysis due to treatment by center interaction.

When data from all centers is analyzed by FDA statisticians, they find that Adapalene is better than vehicle in reduction of total lesions and non-inflammatory lesions, but not better in reduction of inflammatory lesions, at the end of the study. Further, Adapalene is superior to vehicle in physician global evaluation.

It would be advisable to include a Clinical Studies section in the labeling of this product. At a very rough approximation, Adapalene therapy produces about 30-35% reduction in lesion counts after 12 weeks of therapy vs. a 15-20% reduction by vehicle.

d. **Safety:**

i. Adverse Reactions: There were 12 patients (7 in the Adapalene group, 5 in the vehicle group) who discontinued therapy due to adverse events. Four of these (three vehicle, one Adapalene) had reactions or events which were not considered to be related to therapy. These included dyspnea, poison ivy, pregnancy (in a vehicle patient) and malaise.

Of the seven Adapalene patients who discontinued due to an adverse event (7/121 = 6%), there were 2 cases of moderate to severe skin irritation, one of moderate burning, 2 of moderate dermatitis, one each of moderate dry skin and pruritus. The two vehicle patients both experienced moderate skin irritation.

The following table presents the adverse reactions which were probably or possibly related to drug therapy:

Event	Adapalene (n=121)		Vehicle (n=122)	
	n	%	n	%
Miliaria	1	(1)	0	
Skin discoloration	0		1	(1)
Erythema	1	(1)	0	
Sunburn	7	(6)	0	
Dermatitis	2	(2)	1	(1)
Skin discomfort	2	(2)	1	(1)
Skin irritation	2	(2)	1	(1)
Pruritus	1	(1)	1	(1)
Dry Skin	1	(1)	0	
Totals	17	(14)	5	(4)

ii. Erythema, scaling, dryness, pruritus, burning: The percentages of patients in each group who experienced increased, decreased, and unchanged evaluations of each of these phenomena at the end of 12 weeks, as compared to baseline will be presented.

% of Patients at 12 weeks				
Reaction	Treatment	Decreased	Same	Increased
Erythema	Adapalene	10%	67%	23%
	Vehicle	13%	76%	11%
Scaling	Adapalene	2%	81%	17%
	Vehicle	7%	91%	2%
Dryness	Adapalene	1%	88%	11%
	Vehicle	8%	84%	8%
Pruritus	Adapalene	4%	87%	9%
	Vehicle	7%	80%	13%
Burning	Adapalene	0	94%	6%
	Vehicle	2%	91%	7%

Safety Comment: Six percent of the Adapalene patients who entered the study discontinued because of an adverse event; and 14% of the Adapalene patients reported some type of reaction. The most frequent reaction seen was sunburn, which is often seen in association with topical retinoid therapy. About one quarter of the adapalene patients experienced increased facial erythema as compared to baseline after 12 weeks of therapy.

C. Positive Controlled Studies: The sponsor has identified 3 of the submitted active controlled studies as "pivotal", including the dose-ranging study.

1. (pivotal) Study Title: Bicenter Clinical Study of the Safety and Efficacy of CD271 Lotions, 0.03% or 0.1% Compared with 0.025% Tretinoin Gel - Study Report PH87027

Investigators: C. Beylot, M.D.
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Method:

a. Study Design: This was a two center, randomized, evaluator - blind, parallel-group comparison of the effectiveness and safety of Adapalene Lotion 0.1%, Adapalene Lotion 0.03% and Aberel (tretinoin) Gel, 0.025%, manufactured by It is not clear what differences may exist between the product and Retin-A Gel 0.025% which is approved in this country.

b. Patient Selection: Patients of both sexes, aged 13-30 years, were enrolled. These patients were to have Grade 1 through 3 facial acne on the Cunliffe scale (this is mild to moderate acne). The female patients were required to use adequate birth control during the study and for one month after the end of the study.

c. Patient Exclusions: Exclusions where those with acne conglobata, acne fulminans, acne secondary to another disease, and patients with underlying systemic disease.

d. Dosage and duration of treatment: Applications were to be made once daily to the face by the patients (this was an outpatient study) for 12 weeks. Amounts were to be a "pea-size" portion of gel, or 15 drops of lotion.

e. Effectiveness Parameters: The patients were to be evaluated at baseline and at 1, 2, 4, 8, and 12 weeks. The primary effectiveness parameter measured was facial lesions (comedones,

papules, pustules, nodules, cysts.) A global evaluation was also done on a scale from 0 to 3, but the definitions for the scores are not given.

f. Safety Evaluation:

i. Patients were examined for adverse reactions during the course of the study.

ii. Erythema, scaling,pruritus, burning and skin dryness were evaluated on a scale from 0 = none to 3 = severe.

Results:

a. Evaluable Patients: There were 42 patients who entered the study. One patient left the study voluntarily. She was on the 0.1% Adapalene product but did not feel that there was any improvement in her condition. Four other patients failed to complete any return visits, or only completed some. Therefore, the investigators only considered 37 patients to be evaluable. These were distributed as follows:

Investigators			
Treatment	Dr. Boylot	Dr. Meyrandier	Total
0.1% Adapalene	2	10	12
0.03% Adapalene	3	10	13
0.025% Tretinoin	3	9	12

b. Demographics: The demographics for the evaluable patients are as follows (all were Caucasian):

		0.1% Adapalene	0.03% Adapalene	0.025% Tretinoin
Mean Age (yrs)		17.3	18.3	16.9
Sex:	Male	2	6	7
	Female	10	7	5

c. Effectiveness: Results are given at the end of 12 weeks and at endpoint (last valid patient visit).

i. Global grade: The sponsor has provided only mean scores at each visit. No definition is provided for the numerical scores.

Week	Treatment	mean	% Reduction	n
0	0.1% Adapalene	1.4		14
	0.03% Adapalene	1.5		14
	0.025% Tretinoin	1.2		14
12	0.1% Adapalene	0.6	57%	13
	0.03% Adapalene	1.1	27%	13
	0.025% Tretinoin	0.7	42%	11
Endpoint	0.1% Adapalene	0.7	50%	14
	0.03% Adapalene	1.1	27%	13
	0.025% Tretinoin	0.8	33	14

ii. Non-inflammatory lesions (open and closed comedones)

Week	Treatment	Mean	% Reduction	n
0	0.1% Adapalene	47.2		14
	0.03% Adapalene	56.4		14
	0.025% Tretinoin	36.9		14
12	0.1% Adapalene	14.8	69%	13
	0.003 Adapalene	28.0	50%	13
	0.025% Tretinoin	12.8	65%	12
Endpoint	0.1% Adapalene	15.9	66%	14
	0.03% Adapalene	28.0	50%	13
	0.025% Tretinoin	12.5	66%	14

iii. Inflammatory lesions (papules, pustules, nodules, cysts)

Week	Treatment	Mean	% Reduction	n
0	0.1% Adapalene	26.4		14
	0.03% Adapalene	33.9		14
	0.025% Tretinoin	33.3		14
12	0.1% Adapalene	11.9	55%	13
	0.03 Adapalene	22.5	34%	13
	0.025% Tretinoin	18.0	46%	12
Endpoint	0.1% Adapalene	13.1	50%	14
	0.03 Adapalene	22.5	34%	13
	0.025% Tretinoin	16.6	50%	14

iv. Total lesions (inflammatory and non-inflammatory)

Week	Treatment	Mean	% Reduction	n
0	0.1% Adapalene	73.6		14
	0.03% Adapalene	90.4		14
	0.025% Tretinoin	70.2		14
12	0.1% Adapalene	26.7	64%	13
	0.03 Adapalene	50.5	46%	13
	0.025% Tretinoin	30.8	56%	12
Endpoint	0.1% Adapalene	28.9	61%	14
	0.03% Adapalene	50.5	46%	13
	0.025% Tretinoin	29.1	59%	14

d. **Safety:**

i. Adverse Reactions: No spontaneous reactions were reported during the course of the study.

ii. Erythema, scaling, pruritus, burning and skin dryness: The sponsor has presented the data as the percentages of patients in each group with the possible scores (0-3) at 12 weeks. N.D. signifies no data available.

% of Patients at 12 Weeks							
Reaction	Treatment	N.D.	0	1	2	3	N
Burning	0.1% Adapalene	7%	64%	29%	0	0	14
	0.025% Tretinoin	14%	57%	29%	0	0	14
	0.03% Adapalene	7%	64%	7%	21%	0	14
Dryness	0.1% Adapalene	7%	0	43%	50%	0	14
	0.025% Tretinoin	14%	36%	14%	36%	0	14
	0.03% Adapalene	7%	14%	29%	29%	21%	14
Erythema	0.1% Adapalene	7%	86%	7%	0	0	14
	0.025% Tretinoin	14%	50%	21%	14%	0	14
	0.03% Adapalene	7%	50%	43%	0%	0	14
Pruritus	0.1% Adapalene	7%	71%	21%	0	0	14
	0.025% Tretinoin	14%	79%	7%	0	0	14
	0.03% Adapalene	7%	50%	36%	7%	0	14
Scaling	0.1% Adapalene	7%	21%	14%	50%	7%	14
	0.025% Tretinoin	14%	21%	36%	29%	0	14
	0.03% Adapalene	7%	21%	36%	29%	7%	14

Comment: This study may not be accepted as pivotal, primarily because the number of patients in each test group is so small. The study suggests that 0.1% Adapalene is comparable in effect to 0.025% Tretinoin, although it is not clear that the Tretinoin product used in the study is the same as the one approved in the U.S.

2. (pivotal) Study Title: Clinical Safety and Efficacy Comparison of Topical CD271 Lotion, 0.1% with Retin-A Gel in patients with Acne Vulgaris-Study Report C-88-26.

Investigators:

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Method:

a. Study Design: This was a multicenter, double-blind, randomized, parallel-group comparison of the safety and effectiveness of Adapalene Lotion, 0.1% and Retin-A (tretinoin) Gel, 0.025% in acne vulgaris.

b. Patient Selection: The patient selection criteria were the same as for Study B.5 (Study Report C-88-27) above.

c. Patient Exclusions: The patient exclusions were the same as for Study B.5 (Study Report C-88-27) above.

d. Dosage and duration of treatment: Applications were to be made once daily to the face and other affected areas by the patients (this was an outpatient study) for 12 weeks. The protocol provided for less frequent dosing, if necessary.

e. Effectiveness parameters: The effectiveness parameters were the same as for Study B.5 (Study Report C-88-27) above.

f. Safety Evaluation: The safety parameters evaluated were the same as for Study B.S. (Study Report C-88-27) above, except that blood samples were collected at 2 centers (Drs. Berger and Chalker) at baseline and study completion to assess systemic absorption and possible toxicity of adapalene.

Results:

a. Evaluable patients: There were 297 patients enrolled into the study (149 Adapalene, 148 Retin-A). All patients were evaluable for safety.

All patients who completed at least 4 weeks of therapy were considered to be evaluable for efficacy. The following table presents the number of patients per investigator who were enrolled in the study is well as the number of patients who completed the entire 12 week study and the number of patients evaluable for efficacy (had at least four weeks of therapy).

Investigator	Treatment Group	Patients Entering Study	Patients Discontinuing Early	Patients Completing Study	Patients Evaluable for Efficacy
Smith	Adapalene	13	6	7	8
	Retin-A	13	6	7	9
Milliken	Adapalene	20	2	17	19
	Retin-A	20	2	18	19
Swinyer	Adapalene	20	1	19	19
	Retin-A	20	2	18	19
Ellis	Adapalene	20	8	10	15
	Retin-A	20	3	16	18
Katz	Adapalene	20	4	16	18
	Retin-A	20	1	19	19
Berger	Adapalene	18	4	14	14
	Retin-A	18	2	17	18
Chalker	Adapalene	20	7	12	15
	Retin-A	20	4	16	18
Lederman	Adapalene	18	3	15	15
	Retin-A	17	2	15	16
Totals	Adapalene	149	35	110	123
	Retin-A	148	22	126	136

The following table presents the reasons for discontinuance by treatment group:

Reason for Discontinuance	Adapalene	Retin-A
Adverse Event	10	5
Patient Request	5	0
Lost to follow-up	16	12
Noncompliant	1	1
Other	3	4
Total	35	22

The patients who discontinued due to adverse events will be discussed in the safety evaluation below.

There were seven Adapalene patients and five Retin-A patients who were protocol violations because they did not have the minimum required number of inflammatory or noninflammatory lesions for study entrance. The sponsor has left these patients in the efficacy analysis. Review of the line listings indicates that this is acceptable in that the protocol deviations

roughly balance in each group. It is not expected that these deviations could influence the final outcome of the study.

There were eleven Adapalene patients and twelve Retin-A patients who were protocol violations because they took oral antibiotics during the study. Of these, four Adapalene and five Retin-A patients took the drugs at or near the end of the study, which may have affected the most important evaluations from the standpoint of efficacy. These patients have been left in the efficacy analysis. The sponsor was asked to re-analyze the data to omit patients who took oral antibiotics. See the Addendum at the end of this review for the results of that analysis.

b. Demographics: The demographics for the efficacy evaluable patients are as follows:

Characteristics	Adapalene	Retin-A
No. of Subjects	123	136
Sex		
Male	63 (51%)	71 (52%)
Female	60 (49%)	65 (48%)
Age (yr) - Mean	18.5	18.4
Race		
White	108 (88%)	112 (82%)
Black	14 (11%)	19 (14%)
Hispanic	1 (1%)	5 (4%)

c. Effectiveness: Results are presented at the end of 12 weeks of therapy and at "Endpoint".

The reviewers have checked the line listings and are in agreement with the sponsor's representation of the data.

i. Physicians global evaluation

The data has been transformed from the Cunliffe scores to the 4-point scale scores.

Week	Treatment	1	2	3	n
0	Adapalene	0	118 (96%)	5 (4%)	123
	Retin-A	0	127 (93%)	9 (7%)	136
12	Adapalene	53 (48%)	56 (51%)	1 (1%)	110
	Retin-A	61 (48%)	63 (50%)	2 (2%)	126
Endpoint	Adapalene	58 (47%)	62 (51%)	3 (2%)	123
	Retin-A	64 (47%)	70 (52%)	2 (2%)	136

ii. Non-inflammatory lesions (open and closed comedones)

Mean lesion counts and % Reduction			
Week	Treatment	Mean	N
0	Adapalene	50.3	123
	Retin-A	52.1	136
12	Adapalene	21.3 (58%)	111
	Retin-A	23.7 (55%)	126
Endpoint	Adapalene	22.5 (55%)	123
	Retin-A	25.1 (52%)	136

iii. Inflammatory lesions (papules, pustules, nodules, cysts)

Mean lesion counts and % Reduction			
Week	Treatment	Mean	n
0	Adapalene	27.4	123
	Retin-A	28.1	136
12	Adapalene	14.7 (46%)	111
	Retin-A	14.1 (49%)	126
Endpoint	Adapalene	14.8 (46%)	123
	Retin-A	15.4 (45%)	136

iv. Total lesions (inflammatory and non-inflammatory)

Mean lesion counts and % reduction			
Week	Treatment	Mean	n
0	Adapalene	77.7	123
	Retin-A	80.2	136
12	Adapalene	36.0 (54%)	111
	Retin-A	37.8 (53%)	126
Endpoint	Adapalene	37.3 (52%)	123
	Retin-A	40.5 (50%)	136

Efficacy comment: There is no apparent difference between the two medications in effectiveness. It is interesting that the mean lesion counts for both groups decreased by about 50% in this study, while in the vehicle-controlled studies, the Adapalene lesion counts fell by 25% and 33% when the product was used in similar fashion.

It is common to see greater improvement in the patients in positively controlled dermatologic studies than in vehicle controlled studies. The reason for this is not immediately clear, unless the investigators expect to see more improvement if they are aware that all patients are receiving an active medication. However, it is still difficult to see why lesion counts, a completely objective parameter, should be influenced by investigator expectation. From a clinical standpoint, one would be much happier with a product which causes a reduction of one-half in lesion count as compared to one which causes a one-third reduction.

There was no obvious investigator x treatment interaction in this study.

Seventy-two patients volunteered for treatment with Adapalene Lotion up to an additional nine months. Although the primary purpose of this extension was safety rather than efficacy, the sponsor states that in general the patients maintained a level status of improvement from the end of the controlled study (3 months) to the end of the year.

d. Safety:

i. Adverse Reactions: There were 18 patients (12 in the Adapalene group, 6 in the Retin-A group) who discontinued the study at some point. Three of these patients (2 Adapalene, 1 Retin-A) discontinued during the protocol extension (open) part of the study. Since all patients were on Adapalene during the open study the two dermatologic reactions were due to Adapalene (one case of combined skin discomfort, dry skin and erythema, and one of dryness). The other discontinuance in the open part of the study was due to an unrelated infection.

Of the remaining fifteen discontinuances due to adverse events, ten were in the Adapalene group. Three of these were probably not related to drug-"cold syndrome", herpes zoster and accidental injury. The remaining reactions in the Adapalene group, probably or possibly related to drug, were four cases of skin discomfort, erythema and dry skin, two of acne flare, and one of pityriasis rosea. Of the five discontinuances in the Retin-A group, one report of herpes zoster was probably not related to drug. The other four reactions in the Retin-A group, probably or possibly related to drug, were three cases of acne flare and one of skin discomfort, irritation and facial edema.

The following table presents the adverse reactions which were probably or possibly related to drug therapy:

	Adapalene (n=149)		Retin-A (n=148)	
Event	N	%	n	%
Skin discomfort	11	(7)	5	(3)
Erythema	6	(4)	2	(1)
Dry Skin	6	(4)	3	(2)
Pruritus	3	(2)	1	(.6)
Sunburn	1	(.6)	2	(1)
Skin irritation	2	(1)	1	(.6)
Acne flare	2	(1)	3	(2)
"Dermatitis"	1	(.6)	0	
Excoriation	0		1	(.6)
Facial edema	0		1	(.6)
Pityriasis rosea	1	(.6)	1	(.6)
Total	33	(21)	20	(13.5)

ii. Dose alterations: During the course of the 12 week study, the investigators found it necessary to lessen the frequency of application in 21 Adapalene patients and 22 Retin-A patients because of irritation, etc.

iii. Erythema, oiliness, scaling, dryness, burning, pruritus: The percentages of patients in each group who experienced increased, decreased, and unchanged evaluations of each of these phenomena at the end of 12 weeks will be presented.

% of Patients at 12 Weeks				
Reaction	Treatment	Decreased	Same	Increased
Erythema	Adapalene	17%	63%	20%
	Retin-A	20%	63%	17%
Oiliness	Adapalene	47%	47%	6%
	Retin-A	44%	51%	5%
Scaling	Adapalene	4%	50%	46%
	Retin-A	2%	50%	48%
Dryness	Adapalene	5%	46%	49%
	Retin-A	6%	54%	41%
Burning	Adapalene	5%	79%	16%
	Retin-A	2%	88%	10%
Pruritus	Adapalene	5%	72%	23%
	Retin-A	2%	89%	9%

Safety Comment: Five percent of the Adapalene patients who entered the study discontinued because of an adverse event possibly or probably related to therapy, compared to 3% in the Retin-A group. Twenty-one percent of the Adapalene patients reported some type of reaction vs. 13.5% in the Retin-A group. The most frequent reaction seen in association with Adapalene was skin discomfort. More patients experienced increased pruritus during therapy on Adapalene (23%) than on Retin-A (9%).

No significant changes from baseline were found in the patients who had blood samples drawn for absorption, blood chemistries, urinalysis, etc.

3. (pivotal) Study Title: Clinical Safety and Efficacy Evaluation of 0.1% CD 271 Lotion vs 0.025% Retin-A Gel - Study Report CR 88043

Investigators:

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Method:

- **Study design:** This was a multicenter, randomized, double-blind, parallel-group comparison of the effectiveness and safety of Adapalene Lotion 0.1% and Retin-A (tretinoin) Gel, 0.025% in acne vugaris.

b. **Patient selection:** The patient selection criteria were the same as for study B.5 (Study Report C-88-27) above.

c. **Patient exclusion:** The patient exclusions was the same as for study B.5 (Study Report C-88-27) above.

d. **Dosage and duration of treatment:** Applications were to be made once daily to the face and other affected areas by the patients (this was an outpatient study) for 12 weeks.

e. **Effectiveness parameters:** The patients were evaluated at baseline and at 1, 2, 4, 8 and 12 weeks. The parameters evaluated were the same as for study B.5 (Study Report C-88-27) above, although there was no provision for extension of the protocol beyond 12 weeks.

Results:

a. **Evaluable patients:** There were 245 patients enrolled in the study (126 Adapalene, 112 Retin-A). All patients were evaluable for safety.

All patients who completed at least 4 weeks of the study were considered to be evaluable for efficacy. The following table presents the number of patients per investigator who were enrolled in the study, as well as the number of patients who completed the entire 12 week study (the number of patients evaluable for efficacy was the same as the number of patients who completed the study, except for 2 Adapalene patients at an eleventh center who were excluded because they were the only ones at that center), and the number of patients evaluated at week 12.

Investigator	Treatment	Patients Enrolled	Patients Discontinuing	Patients that Completed Study	Patients Evaluable for Efficacy at Week 12
Cunliffe	Adapalene	22	0	22	21
	Tretinoin	22	0	22	21
Jones	Adapalene	7	2	5	3
	Tretinoin	6	0	6	5
MacDonald	Adapalene	17	1	16	13
	Tretinoin	15	2	13	11
Plewig	Adapalene	3	1	2	0
	Tretinoin	2	2	0	0
Orfanos	Adapalene	8	0	8	7
	Tretinoin	8	0	8	8
Privat	Adapalene	20	2	18	14
	Tretinoin	20	2	18	16
Amblard	Adapalene	10	1	9	7
	Tretinoin	10	0	10	10
Bruneriere	Adapalene	9	2	7	6
	Tretinoin	7	0	7	6
Caputo	Adapalene	23	0	23	22
	Tretinoin	23	2	21	19
de la Brassine	Adapalene	7	3	4	1
	Tretinoin	6	2	5	3
Total	Adapalene	126	12	114	94
	Tretinoin	119	9	110	99

The following table presents the reasons for discontinuation by treatment group:

Reason for Discontinuation	Adapalene	Retin-A
Treatment failure	1	2
Adverse event	7	2
Lost to follow-up	3	2
Non-compliant	1	2
Other	0	1
Total	12	9

The patients who discontinued due to adverse events will be discussed in the safety evaluation below.

There were 8 patients in the Adapalene group and 10 in the Retin-A group who did not meet the minimum requirement for lesion counts. Since these protocol violations roughly balance in each group the sponsor has left the patients in the efficacy data base. This is acceptable.

Four patients took oral antibiotics during the course of the study. These patients have been left in the data base. Since they are so few, this is acceptable.

b. Demographics: The demographics for all patients who entered the study are as follows:

Characteristics	Adapalene	Retin-A
No. of Subjects	126	119
Sex		
Male	76 (60%)	77 (65%)
Female	50 (40%)	42 (35%)
Age (yr) Mean	19.0	18.9
*Racial demographics are not given.		

Effectiveness: Results are given at the end of 12 weeks of therapy and at "Endpoint".

The reviewers have checked the line listings and are in agreement with the sponsors presentation of the data.

i. Physician global evaluation

The sponsor has provided global data only in terms of the mean global score (whether it is the Cunliffe score or the 4 point scale is not specified) at each evaluation. The difficulty with this presentation is that it does not give an impression of the distribution of scores throughout the patient populace. This distribution of scores is important to be sure that mean scores are not disguising an unusual distribution of effectiveness (e.g., one treatment group has more people at either end of the data spread than does the other treatment group, even though the mean data indicates the treatments are similar). It is preferred that at least one data presentation for any study reflect the outcomes of the individual patients, rather than the mean outcome.

Mean global grade and % reduction			
Week	Treatment	Mean	N
0	Adapalene	1.6	112
	Retin-A	1.8	110
12	Adapalene	0.8 (50%)	94
	Retin-A	0.8 (56%)	98
Endpoint	Adapalene	0.8 (50%)	112
	Retin-A	0.8 (50%)	110

ii. Non-inflammatory counts and % reduction

Mean lesion counts and % reduction			
Week	Treatment	Mean	N
0	Adapalene	64.8	112
	Retin-A	67.8	110
12	Adapalene	17.7 (73%)	94
	Retin-A	20.7 (69%)	99
Endpoint	Adapalene	18.3 (72%)	112
	Retin-A	20.5 (70%)	110

iii. Inflammatory lesions (papules, pustules, cysts, nodules)

Mean lesion and % reduction			
Week	Treatment	Mean	N
0	Adapalene	33.3	112
	Retin-A	36.2	110
12	Adapalene	13.3 (60%)	94
	Retin-A	12.6 (65%)	99
Endpoint	Adapalene	12.6 (62%)	112
	Retin-A	12.2 (66%)	110

iv. Total lesions (inflammatory and non-inflammatory)

Mean lesion counts and % reduction			
Week	Treatment	Mean	N
0	Adapalene	98.1	112
	Retin-A	104.0	110
12	Adapalene	30.9 (69%)	94
	Retin-A	33.3 (68%)	99
Endpoint	Adapalene	30.9 (69%)	112
	Retin-A	32.6 (69%)	110

Efficacy comment: There is no apparent difference between the two medications in effectiveness. Once again, the decrease in mean lesion counts is measurably greater than in the pivotal vehicle-controlled study, and is in fact greater than the decrease seen in a virtually identical positive-controlled study performed in this country. Very roughly, the decrease in mean total lesion counts in the vehicle-controlled study for Adapalene was 30%, while this value was 50% in the U.S. positive-control study and 70% in the European positive-control study. There were more lesions at baseline in the European positive-control study. There were more no obvious treatment x investigator interactions in the study.

This study may be accepted as supportive, principally because the physician global evaluation has not been presented in a manner which allows analysis of the score frequencies. This data could be obtained, but it is unnecessary because the U.S. positive-control study (C-88-26) is acceptable as a pivotal study.

d. Safety:

i. Adverse reactions: There were seven Adapalene patients and two Retin-A patients who discontinued the study because of "skin intolerance", which was not further described, with the following exceptions: one Adapalene and one Retin-A patient had "irritation dermatitis". No other spontaneous adverse events are reported, which is unusual in studies of this type.

ii. Erythema, dryness, scaling, pruritus, burning, oiliness: The sponsor has presented the data as percentages of patients in each group with the possible scores (0-3) at 12 weeks. N.D. signifies no data available.

% of Patients at 12 Weeks							
Reaction	Treatment	N.D.	0	1	2	3	N
Erythema	Retin-A	12%	40%	34%	12%	2 %	119
	Adapalene	17%	41%	30%	10%	1 %	126
Dryness	Retin-A	11%	39%	33%	12%	5 %	119
	Adapalene	17%	43%	23%	10%	6 %	126
Scaling	Retin-A	11%	45%	33%	10%	2 %	119
	Adapalene	17%	47%	21%	13%	2 %	126
Pruritus	Retin-A	11%	78%	7%	3%	0	119
	Adapalene	17%	60%	15%	6%	1 %	126
Burning	Retin-A	11%	64%	20%	5%	0	119
	Adapalene	17%	66%	10%	5%	2 %	126
Oiliness	Retin-A	11%	62%	22%	4%	0	119
	Adapalene	17%	45%	33%	5%	2 %	126

Safety Comment: Approximately 6% of the Adapalene patients who entered the study discontinued because of an adverse event, compared to 2% in the Retin-A group. No other adverse reactions were reported during the study, which is highly unusual. More Retin-A patients had no pruritus and oiliness at the end of therapy than did Adapalene patients.

D. Safety Summary: The total number of acne patients exposed to Adapalene Solution during clinical development was 571. An additional 199 healthy volunteers were exposed to the drug during Phase I testing. There were no adverse events attributable to drug therapy reported as a result of the Phase I trials.

I. The sponsor specifically gathered data concerning skin symptoms which are commonly associated with retinoid therapy. Since these reactions were not spontaneously reported, and it is common practice to report only spontaneous reactions in the ADVERSE REACTIONS section of the labeling, it is felt that the data for the effects specifically included in the protocols (erythema, oiliness, etc.) should not be included in the spontaneous reports of adverse reactions in the labeling, but rather in the CLINICAL STUDIES section. The following summary outlines the relevant findings for the reactions which were part of the safety data information gathered per the protocols:

1. In the small vehicle-controlled study performed by Dr. Jablonska, (Study Report PC-86030), nearly all patients on the active product were found to have erythema, dryness, burning or pruritus at some time during the study vs. about half the vehicle patients.

2. In the smaller multicenter vehicle-controlled study (Study Report C-88-27), about one-third of the Adapalene patients experienced increased erythema, dryness and pruritus at 12 weeks as compared to baseline. Dryness was increased in the vehicle group in a manner similar to that experienced by the active group, but the active group experienced more increased erythema (36% vs. 15%) and pruritus (27% vs. 11%) than did the vehicle group.

3. In the larger multicenter vehicle-controlled study (Study Report 9104-CD271L-EV), about one-fifth of the active group experienced increased erythema and scaling at 12 weeks as compared to baseline, and for both symptoms the active group reported this more often than the vehicle group (erythema 23% vs. 11% and scaling 17% vs. 2%).

4. In the domestic positive control multicenter study (Study Report C-88-26), about half of both groups reported increased scaling and dryness at 12 weeks as compared to baseline. The only parameter in which the groups displayed a difference was pruritus, which was increased more often at 12 weeks in the Adapalene group than in the Retin-A group (23% vs. 9%).

5. In the European positive control multicenter study (Study Report CR 88043), the only differences seen were in pruritus (78% of Retin-A patients vs. 60% of Adapalene patients had no pruritus at 12 weeks) and oiliness (62% of Retin-A patients vs. 45% of Adapalene patients had no oiliness at 12 weeks).

II. In Phase 2 and 3 trials, a total of 184 patients were exposed to Adapalene Solution in European trials and a total of 325 patients were exposed to the drug in U.S. trials. The rates of spontaneous reactions in the U.S. and European studies were quite different, and they will be reported separately.

In the European studies, there were $^{8}/_{184}$ = 4% adverse reactions reported as associated with Adapalene Solution, $^{2}/_{131}$ = 2% adverse reactions reported as associated with Retin-A, and no adverse reactions reported in 31 vehicle patients. The reactions reported for Adapalene in the European trials were as follows:

Event	Number
Skin discomfort	4
Irritation dermatitis	2
Forehead eczema	1
Vesicobullous eruption	1

In the U.S. trials, there were $^{65}/_{325}$ = 20% adverse events reported as possibly or probably related to Adapalene solution. Comparable rates for the vehicle were $^{11}/_{177}$ = 6% and for Retin-A, $^{20}/_{148}$ = 13.5%. The reactions reported for Adapalene in the U.S. trials were:

Event	Number
Erythema	12
Skin discomfort	18
Pruritus	7
Dry Skin	8
Dermatitis	4
Sunburn	8
Miliaria	1
Skin irritation	4
Acne flare	2
Pityriasis rosea	1

III. On August 27, 1993, the sponsor submitted the 4 month safety update for the NDA. No new patients have been exposed to Adapalene Solution, but clinical development studies are continuing on new cream and gel formulations. The adverse events seen with the new formulations are similar to those seen with the solution, and are somewhat lower in frequency.

Comment: These results indicate that Adapalene Solution has the potential to produce cutaneous reactions of the type and frequency often seen in connection with topical retinoid therapy. It seems reasonable to include suggestions in the labeling to use sunscreens in conjunction with the product, such as is done with Retin-A.

Preliminary review of the pharmacokinetic and animal toxicology data indicate that Adapalene is poorly absorbed through human skin and is not a potent teratogen in animals when applied topically. Nevertheless, these impressions must be corroborated by the proper FDA reviewers.

It is noted that all clinical studies required the female test subjects to have negative pregnancy tests prior to study entrance, and to use positive

birth control during the study and for some time after the study ended. Unless additional data concerning the teratogenic potential of Adapalene is discovered, it is not felt that the female users of the drug must follow these precautions.

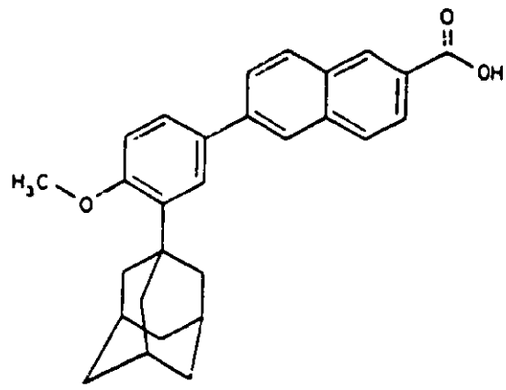
E. **Labeling Review:** The labeling submitted by the sponsor requires extensive revision. Rather than discuss the individual items in question, a draft label will be presented which represents the preferred language.

(TRADE NAME) Solution, 0.1%
(adapalene solution)

FOR TOPICAL DERMATOLOGIC USE ONLY -
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE.

DESCRIPTION: (TRADE NAME) Solution, 0.1% contains adapalene, a synthetic retinoid-like compound. (TRADE NAME) Solution contains adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. It is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula:



CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological animal profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and certain inflammatory process. Mechanistically, adapalene binds to specific retinoid acid nuclear receptors but, unlike tretinoin, does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, current evidence suggests that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. In both *in vivo* and *in vitro* assay models, adapalene inhibits the chemotactic

'directional) and chemokinetic (random) responses of human lymorphonuclear leukocytes; it also inhibits the metabolism of .achidonic acid, by lipoxidation, to inflammatory mediators.

PHARMACOKINETICS: Absorption of adapalene through human skin is low; in clinical trials measurable plasma levels were not detected following chronic topical application. Excretion appears to be primarily by the biliary route.

INDICATIONS AND USAGE: (TRADE NAME) Solution is indicated for the topical treatment of mild to moderate acne vulgaris.

CONTRAINDICATIONS: (TRADE NAME) Solution, 0.1% is contraindicated in individuals who have known or suspected hypersensitivity to adapalene or any of its other ingredients.

PRECAUTIONS: (General): If a reaction suggesting sensitivity or excess irritation occurs, use of the medication should be discontinued and appropriate therapy instituted.

(TRADE NAME) Solution is for external use only. Avoid contact with eyes, lips, angles of the nose, mucous membranes and open wounds. Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus can be expected with the use of (TRADE NAME) Solution. If the degree of the side effect warrants, patients should be directed to discontinue use temporarily, or discontinue use altogether.

Exposure to sunlight, including sunlamps, should be minimized during the use of (TRADE NAME) Solution, and patients with sunburn should be advised not to use the product until fully recovered. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.

Information for Patients: The patient should be instructed to:

1. Use the drug as directed by the physician and avoid contact with the eyes, nose, mouth or mucous membranes.

2. Limit exposure to sunlight as much as possible. Use of sunscreen products and protective clothing over treated areas is recommended. Artificial sunlamps should not be used while undergoing therapy with (TRADE NAME) Solution.

3. Inform the physician if the area of application shows signs of increased irritation or possible sensitization (redness, dryness, scaling, burning or itching).

4. Avoid the use of other medications on the treatment area unless directed by the physician. Non-comedogenic cosmetics should be used. Color cosmetics such as blushes and powders are acceptable, but they should be water-based.

5. No studies have been conducted in humans to establish the safety with (TRADE NAME) Solution in pregnant women. If a patient is pregnant, thinks she is pregnant, or is nursing a baby, the physician should be consulted before using this medication.

Drug Interactions: Potential interactions between (TRADE NAME) Solution and other drugs have not been systematically evaluated. However, concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol or astringents should be used with caution, as they may produce additive irritant effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime studies with adapalene have been completed in mice at topical doses of 0.6, 2 and 6 mg/kg/day and in rats at oral doses of 0.15, 0.5 and 1.5 mg/kg/day and demonstrated no carcinogenic effect. Animal studies have shown an increased tumorigenic risk with the use of related drugs (e.g., tretinoin) when combined with exposure to the ultraviolet (UV) light in sunlight, or from other UV sources. Studies to determine whether adapalene may accelerate the tumorigenic effects of UV radiation have not been conducted. In a series of *in vivo* and *in vitro* animal tests, adapalene did not demonstrate mutagenic or genotoxic activity. Reproductive function and fertility studies were conducted in rats administered oral doses of adapalene in amounts up to 20 mg/kg/day. No effects of adapalene were found on the reproductive performance or fertility of the F_0 males or females. There were also no detectable effects on the growth, development and subsequent reproductive function of the F_1 offspring.

Pregnancy: Teratogenic effects. Pregnancy Category C. *Oral*. Adapalene administered orally at high doses has been shown to be teratogenic in rats and rabbits. *Topical*. Teratology studies performed in rats and rabbits at cutaneous doses from 50 to 200 times the human dose (assuming the human dose to be 500 mg to 2000 mg of 0.1% solution per day) have shown no clear evidence of effects on the fetus *in utero* in the rabbit, and only a minimal increase 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.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (TRADE NAME) Solution is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS:

U.S. Clinical Trials: In controlled clinical trials performed in the United States with (TRADE NAME) Solution, the total incidence of adverse events possibly or probably related to treatment was 20% (65 reports from

325 participants). The most frequent reactions reported were skin discomfort (burning and stinging) in 5.5% of patients, erythema (3.6%), dry skin (2.5%), sunburn (2.5%), pruritus (2%), dermatitis (1%), skin irritation (1%), and acne flare and miliaria in less than 1% of patients.

OVERDOSAGE: Acute overdosage with topical application of adapalene is unlikely due to the limited absorption of topically applied drug and would not be expected to lead to a life threatening situation. The acute oral toxicity of (TRADE NAME) Solution in mice and rats is greater than 10 mL/kg. In the event the product is accidentally ingested, an appropriate method of gastric emptying should be considered.

DOSAGE AND ADMINISTRATION: DIFFERIN Solution should be applied to the affected areas of the face, chest and back once a day before retiring and after washing. A thin film of the solution should be applied, avoiding eyes, lips and mucous membranes.

If the medication is applied excessively, no more rapid or better results will be obtained and adverse reactions may occur.

More than eight weeks of therapy may be required before definite beneficial effects are seen.

With patients for whom it is necessary to temporarily discontinue therapy, therapy may be resumed if it is judged that the patient is able to tolerate the treatment.

HOW SUPPLIED: (TRADE NAME) Solution (adapalene) is supplied in the following sizes:

30 mL glass bottle with applicator - **NDC** 0299-5905-30
60 mL glass bottle with applicator - **NDC** 0299-5905-60

The applicator is designed so that the solution may be applied directly to the involved skin.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Keep container tightly closed and store upright.

CLINICAL STUDIES: The vehicle-controlled clinical study compared (TRADE NAME) Solution to its vehicle for twelve weeks in patients with mild to moderate acne vulgaris. There were 104 evaluable patients in the (TRADE NAME) group and 113 in the vehicle group in this multicenter study. At the end of twelve weeks of therapy, the following results were seen:

i. Physician global evaluation: The global evaluation was made on a scale from 0 = no disease to 4 = worst disease One of the centers in the study is not included in this presentation. There were no grades of 0 or 4 in the study. The numbers 1, 2, and 3 represent mild to moderate acne.

Number of Patients and % of n					
Week	Treatment	1	2	3	N
0	(TRADE NAME)	0	84 (93%)	6 (7%)	90
	Vehicle	0	91 (92%)	8 (8%)	99
12	(TRADE NAME)	36 (44%)	45 (56%)	0	81
	Vehicle	24 (26%)	62 (68%)	5 (6%)	91

ii. Non-inflammatory lesions (open and closed comedones)

Mean lesion counts and % reduction			
Week	Treatment	Mean (%)	N
0	(TRADE NAME)	61.5	104
	Vehicle	65.3	113
12	(TRADE NAME)	38.7 (37%)	95
	Vehicle	55.5 (15%)	105

iii. Inflammatory lesions (papules and pustules)

Mean lesion counts and % reduction			
Week	Treatment	Mean (%)	N
0	(TRADE NAME)	18.0	104
	Vehicle	19.5	113
12	(TRADE NAME)	12.8 (29%)	95
	Vehicle	14.0 (29%)	105

iv. **Erythema, scaling, pruritus, dryness, burning:**

% of Patients at 12 weeks				
Reaction	Treatment	Decreased	Same	Increased
Erythema	(Trade Name)	10%	67%	23%
	Vehicle	13%	76%	11%
Scaling	(Trade Name)	2%	81%	17%
	Vehicle	7%	91%	2%
Dryness	(Trade Name)	1%	88%	11%
	Vehicle	8%	84%	8%
Pruritus	(Trade Name)	4%	87%	9%
	Vehicle	7%	80%	13%
Burning	(Trade Name)	0	94%	6%
	Vehicle	2%	91%	7%

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:

Owen/Galderma Laboratories, Inc.
Fort Worth, Texas 76134 USA

Mfd. by:

DPT Laboratories, Inc.
San Antonio, Texas 78215 USA

Conclusions and Recommendations: This application should be made approvable from a clinical standpoint. The following comments apply:

1. A satisfactory pharmacology review is necessary prior to approval. Specifically, the "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy" subsections of the labeling should be reviewed by the pharmacologist for accuracy.

2. A satisfactory biopharmaceutics review is necessary prior to approval. Specifically, the sponsor's assertions that the drug is poorly absorbed through the skin should be verified, and the PHARMACOKINETICS section of the labeling should be reviewed by the biopharmaceutics reviewer for accuracy.

3. A satisfactory chemistry review is also necessary.

In summary, adapalene appears to be similar in effectiveness and toxicity to 0.025% tretinoin gel. Only mild to moderate acne was studied in the pivotal clinical studies.

In a relatively small (97 evaluable patients) vehicle controlled, parallel group study, no significant differences were found between Adapalene Solution and its vehicle. In a larger (217 patient) study of the same design, Adapalene Solution was found to be superior to vehicle in physician global evaluation, non-inflammatory lesion counts and total lesion counts (but not inflammatory lesion counts).

In a 259 patient parallel-group study comparing Adapalene Solution to Retin-A (tretinoin) Gel 0.025%, there were no significant differences in the effectiveness of the products. It is interesting that in this positively controlled study mean total lesion counts decreased by about 50%, while in the vehicle controlled study mean total lesion counts decreased by about 35%, even through the protocols were identical in terms of frequency of drug application and length of therapy.

About 20% of patients in the U.S. controlled clinical studies reported adverse events. These were local skin reactions commonly seen in topical retinoid therapy.

David Bostwick

See Superior Medical Review Comments
7/5/94
Wiley A. Chambers, M.D.

4/11/96

cc: Orig. NDA
HFD-340
HFD-520/Bostwick
HFD-540/~~Geck~~ FORWARD
HFD-520/Chambers
HFD-520/Timper
HFD-520/Dionne
HFD 540- TOOMBS

ADDENDUM TO CLINICAL REVIEW

APR 11 1996

NDA 20-338 **DATE OF REVIEW:** March 30, 1994

APPLICANT: Owen/Galderma Laboratories, Inc.
P.O. Box 6600
Fort Worth, TX 76115

DRUG: Differin (adapalene) Solution, 0.1%

DATE OF SUBMISSION: The original NDA was submitted March 19, 1993. The amendments reviewed here are dated January 31 and February 28, 1994.

BACKGROUND: Please see the clinical review of the original submission dated August 16, 1993. This review is intended to: (a) update the status of the reviews by other disciplines, (b) review the safety update of February 28, 1994, and (c) make additional data presentations requested by the Acting Division Director, HFD-520, in her secondary review of the application.

MATERIAL REVIEWED:

1. Reviews by other disciplines:

   a) Chemistry: In his review dated November 8, 1993, the chemist, Mr. Timper noted that the application is not approvable due to deficiencies in environmental assessment, methods validation, and establishment inspections.

   b) Biopharmaceutics: In her review dated October 1, 1993, the reviewer, Dr. Dorantes, found that the application is approvable with labeling changes. The proposed package insert in the original clinical review should therefore be revised, i.e., the **Pharmacokinetics** subsection of the **CLINICAL PHARMACOLOGY** section should read as follows:

   "**Pharmacokinetics:** The absorption of adapalene through human skin is low. Data from clinical trials where the systemic absorption of adapalene was monitored in acne patients after multiple topical applications of (TRADE NAME) Solution, 0.1% do not show any measurable plasma levels of adapalene at a detection limit of 1 ng/mL.

   In a study conducted in four male volunteers, a single application of 0.5 mL of a solution containing 0.1% ^{14}/C-adapalene did not result in any measurable adapalene plasma levels. However, some traces of radioactivity were found in the feces of each subject,

mainly between the third and sixth day following drug administration. The amount measured accounted for 0.02-0.06% of the administered dose of adapalene.

In vitro studies revealed that more than 99% of adapalene was bound in human whole blood. About 26% was bound to erythrocytes with lipoprotein and human serum albumin accounting for the majority of plasma binding."

c) Pharmacology: This is not yet available. Comment is required from the pharmacologist concerning the **Carcinogenesis, Mutagenesis, Impairment of Fertility** and **Pregnancy** subsections of the labeling.

2. Safety Update: The applicant indicates that there is no new information to report concerning Adapalene Solution, 0.1%. The applicant is presently investigating or has submitted NDA's for three additional adapalene formulations, i.e., 0.1% & 0.3% gels and a 0.1% cream. Cumulative irritation studies indicate that the 0.3% gel is slightly irritating. In large-scale clinical trials with the cream and gels, the adverse reactions seen were similar to those seen with the solution, and the incidence of these reactions was slightly less than for the solution.

3. Additional data presentations: As a result of her secondary review of the original clinical data for Adapalene Solution, Dr. Gavrilovich requested that the results for studies 9104-CD271L-EV and C-88-26 be represented, excluding all patients who took antibiotics at any point during the study, since these patients were protocol violators.

The following tables compare the results in lesion counts with and without patients who took antibiotics.

STUDY 910-CD271L-EV:

Non-inflammatory Lesions
(open & closed comedones)

		Mean lesion counts and % reduction			
		Original Data		Without Users of Antibiotics	
Week	Treatment	Mean	N	Mean	N
0	Adapalene	61.5	104	61.8	100
	Vehicle	65.3	113	66.0	106
12	Adapalene	38.7 (37%)	95	39.4 (36%)	92
	Vehicle	55.5 (15%)	105	56.5 (14%)	98
Endpoint	Adapalene	40.3 (34%)	102	41.0 (34%)	99
	Vehicle	57.6 (12%)	112	58.7 (11%)	105

Inflammatory Lesions
(papules & pustules)

		Mean lesion counts and % reduction			
		Original Data		Without Users of Antibiotics	
Week	Treatment	Mean	N	Mean	N
0	Adapalene	18.0	104	18.1	100
	Vehicle	19.5	113	19.8	106
12	Adapalene	12.8 (27%)	95	13.0 (28%)	92
	Vehicle	14.0 (29%)	105	14.1 (29%)	98
Endpoint	Adapalene	12.9 (28%)	102	13.1 (28%)	99
	Vehicle	14.1 (28%)	112	14.3 (28%)	105

Total Lesions
(inflammatory & non-inflammatory)

		Mean lesion counts and % reduction			
		Original Data		Without Users of Antibiotics	
Week	Treatment	Mean	N	Mean	N
0	Adapalene	79.5	104	79.9	100
	Vehicle	84.8	113	85.8	106
12	Adapalene	51.5 (35%)	95	52.4 (34%)	92
	Vehicle	69.5 (18%)	105	70.6 (17%)	98
Endpoint	Adapalene	53.2 (33%)	102	54.1 (32%)	99
	Vehicle	71.7 (15%)	112	73.0 (15%)	105

STUDY C-88-26

Non-inflammatory Lesions
(open & closed comedones)

		Mean lesion counts and % reduction			
		Original Data		Without Users of Antibiotics	
Week	Treatment	Mean	N	Mean	N
0	Adapalene	50.3	123	44.2	113
	Retin-A	52.1	136	44.8	125
12	Adapalene	21.3 (58%)	111	17.8 (60%)	102
	Retin-A	23.7 (55%)	126	19.4 (57%)	115
Endpoint	Adapalene	22.5 (55%)	123	18.7 (58%)	113
	Retin-A	25.1 (52%)	136	20.3 (55%)	125

Inflammatory Lesions
(papules & pustules)

		Mean lesion counts and % reduction			
		Original Data		Without Users of Antibiotics	
Week	Treatment	Mean	N	Mean	N
0	Adapalene	27.4	123	25.3	113
	Retin-A	28.1	136	25.0	125
12	Adapalene	14.7 (46%)	111	12.5 (51%)	102
	Retin-A	14.8 (49%)	126	12.4 (52%)	115
Endpoint	Adapalene	14.8 (46%)	123	12.9 (49%)	113
	Retin-A	15.4 (45%)	136	13.1 (50%)	125

Total Lesions
(inflammatory & non-inflammatory)

		Mean lesion counts and % reduction			
		Original Data		Without Users of Antibiotics	
Week	Treatment	Mean	N	Mean	N
0	Adapalene	77.7	123	69.5	113
	Retin-A	80.2	136	70.8	125
12	Adapalene	36.0 (54%)	111	30.3 (57%)	102
	Retin-A	37.8 (53%)	126	31.8 (55%)	115
Endpoint	Adapalene	37.3 (52%)	123	31.6 (55%)	113
	Retin-A	40.5 (50%)	136	33.4 (53%)	125

Comment: Exclusion of patients who took oral antibiotics during the course of the two large pivotal studies does not affect the conclusions drawn in the original review.

CONCLUSIONS AND RECOMMENDATIONS:

This application may be made approvable from a clinical standpoint. Revised draft labeling should be made available to the sponsor which includes the revisions noted in the original clinical review and in section 1(b) above.

Satisfactory chemistry and pharmacology reviews are necessary prior to approval of this NDA.

David C. Bostwick
Clinical Reviewer

See Supervisory Medical Review

Wiley A. Chambers, M.D.
Supervisory Medical Officer

4/11/96

cc: NDA 20-338
HFD-540
HFD-540/SCSO/~~Cook~~ Forman
HFD-540/SCH/DeCamp
HFD-520/CH/Timper
HFD-540/PH/Mainigi
HFD-520/MO/Bostwick
HFD-520/SMO/Chambers
HFD-520/DIR/~~Gavrilovich~~ William
HFD-713/STAT/Daphne
HFD-426/BIOPH/Dorantes
HFD 540 · Toomas
FT/5/6/94/SMChilds

MAY 31 1996

Clinical Team Leader Review of NDA 20-338
Review #2

NDA 20-338
Review #2

Review completed: 4/12/96

Drug name: Differin Solution, 0.1%
Generic name: Adapalene solution

Sponsor: Owen/Galderma Laboratories, Inc.
Fort Worth, TX 76115

Pharmacologic Category: Retinoid

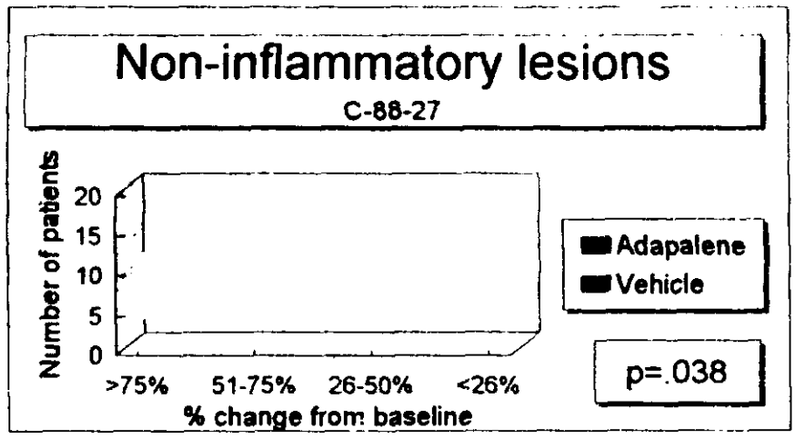
Proposed Indication(s): Treatment of acne vulgaris

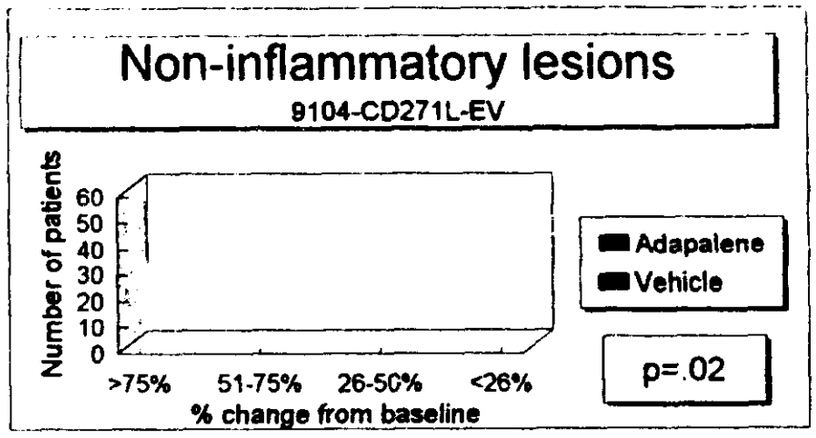
Related Reviews:

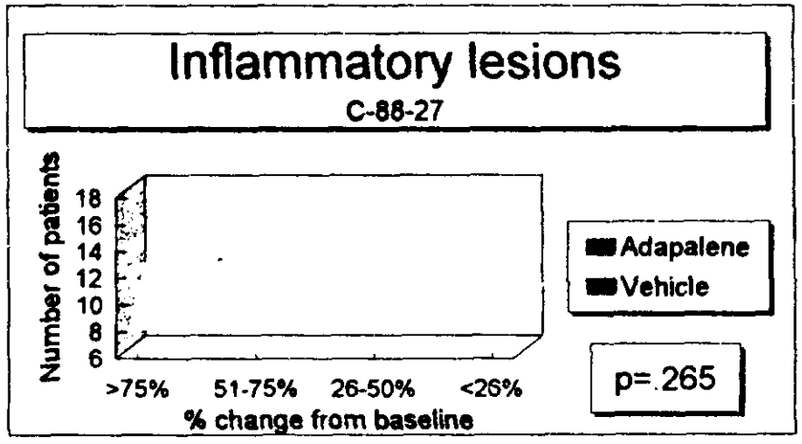
Clinical Review dated	10/ 7/93
Clinical Addendum dated	3/30/94
Supervisory MOR dated	7/ 5/94
Statistical Review dated	11/ 9/93

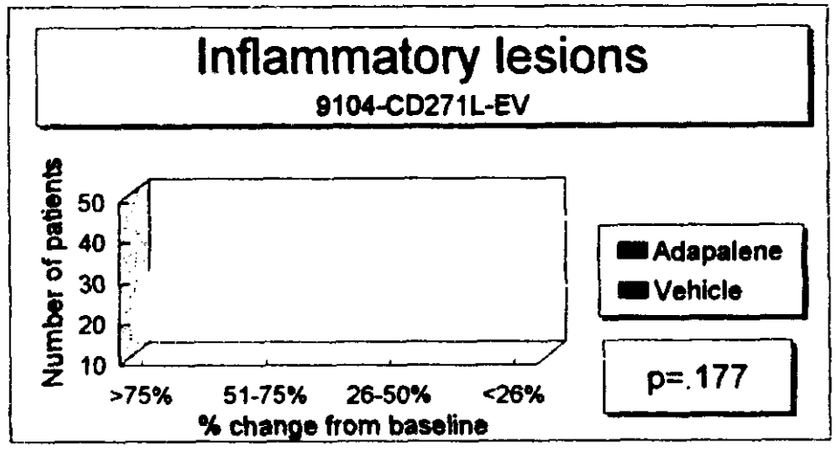
Background:

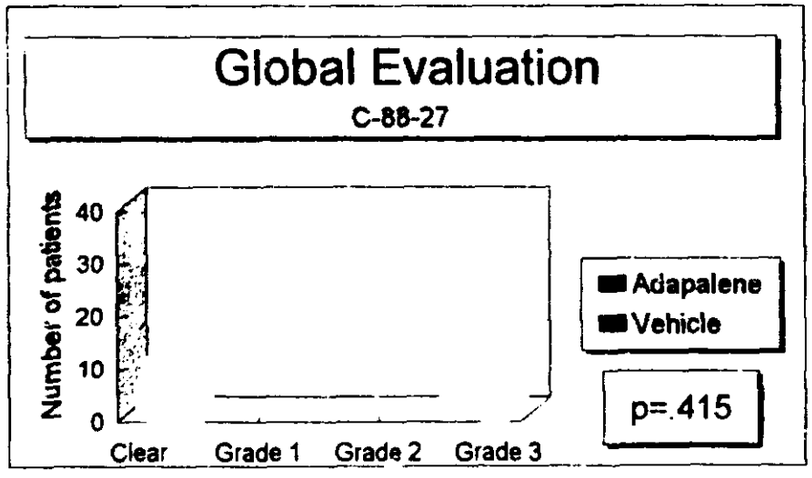
There is an inconsistency between the results as reported in the clinical review and the statistical review. The difference is related to the method of analysis performed. The Supervisory MOR dated 7/5/94 was based on the original MOR. After re-review of that data in conjunction with the statistical review, a determination was made that the more appropriate analysis for these trials is the one performed by the FDA statistical review team.

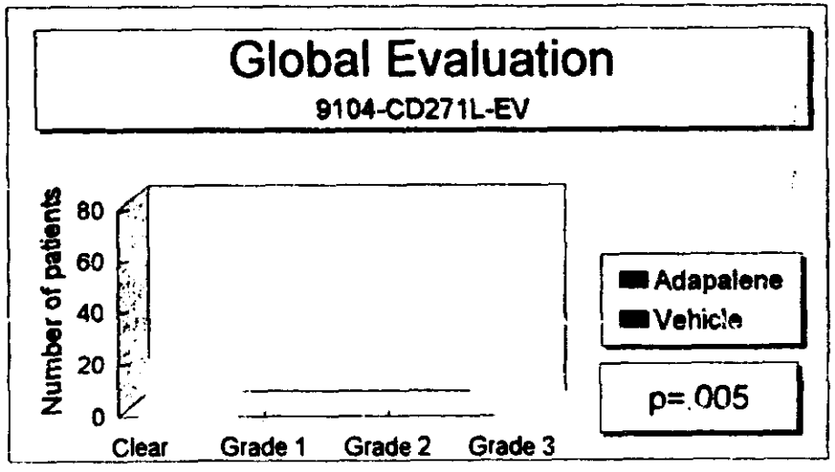

Non-inflammatory lesions
C-88-27
Number of patients
20
15
10
5
0
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Vehicle
p=.038

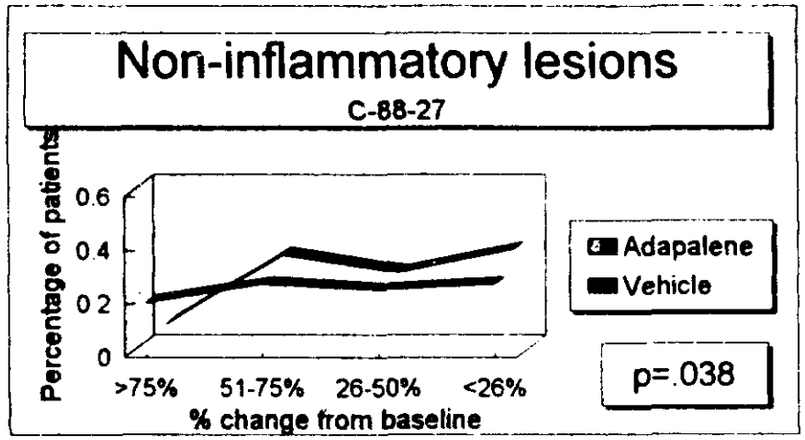

Non-inflammatory lesions
9104-CD271L-EV
Number of patients
60
50
40
30
20
10
0
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Vehicle
p=.02

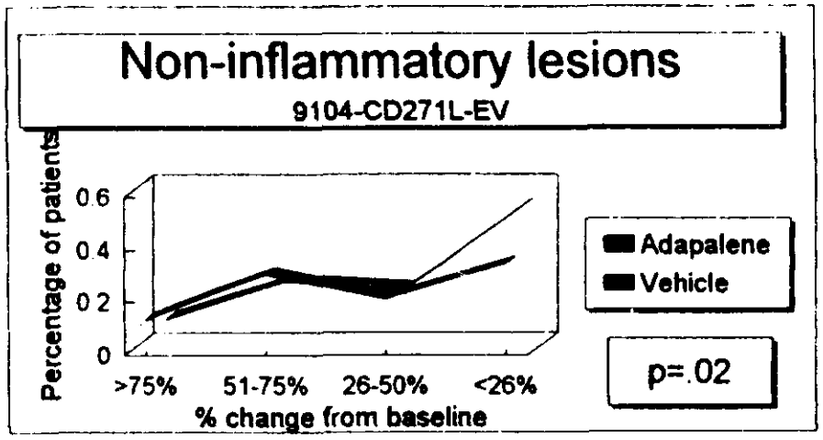

Inflammatory lesions
C-88-27
Number of patients
18
16
14
12
10
8
6
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Vehicle
p=.265

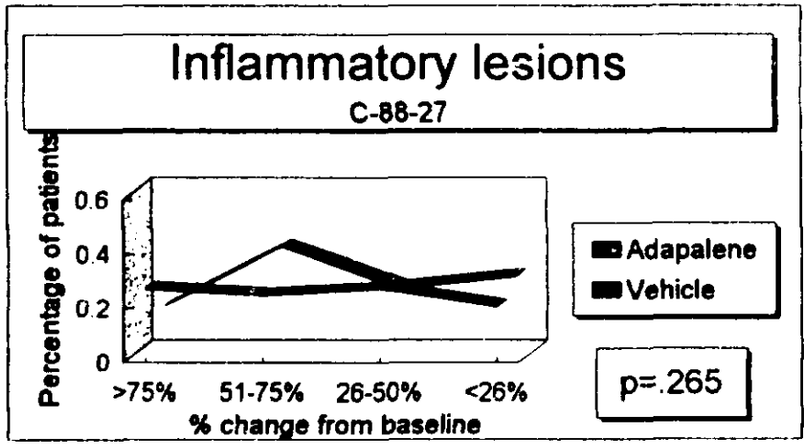

Inflammatory lesions
9104-CD271L-EV
Number of patients
50
40
30
20
10
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Vehicle
p=.177

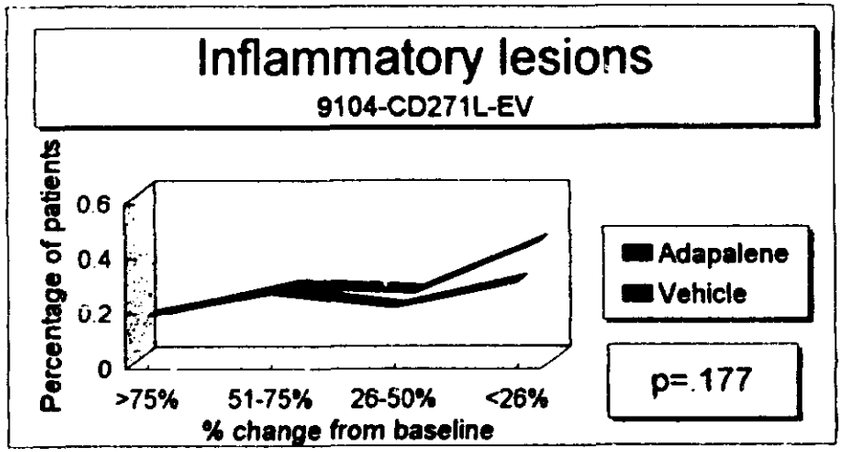

Global Evaluation
C-88-27
Number of patients
40
30
20
10
0
Clear
Grade 1
Grade 2
Grade 3
Adapalene
Vehicle
p=.415

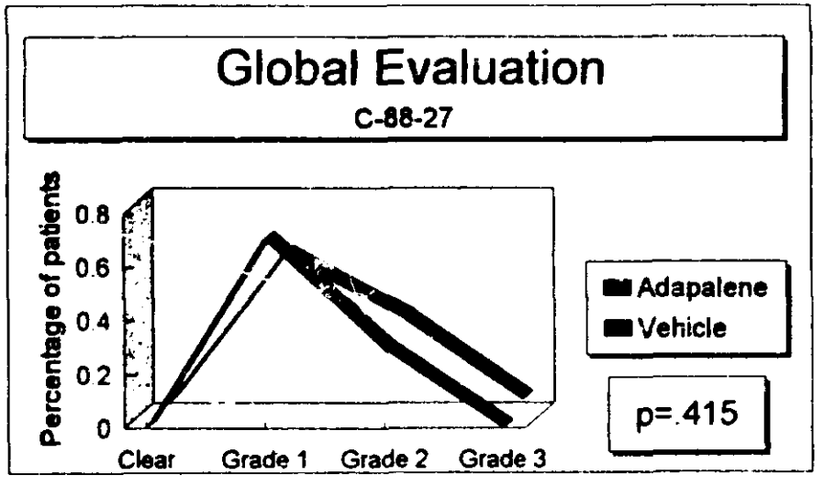

Global Evaluation
9104-CD271L-EV
Number of patients
80
60
40
20
0
Clear
Grade 1
Grade 2
Grade 3
Adapalene
Vehicle
p=.005

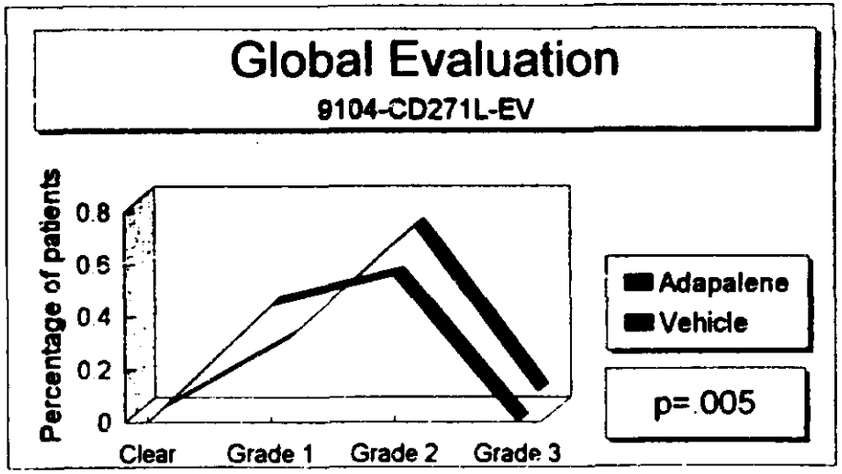

Non-inflammatory lesions
C-88-27
Percentage of patients
0.6
0.4
0.2
0
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Vehicle
p=.038

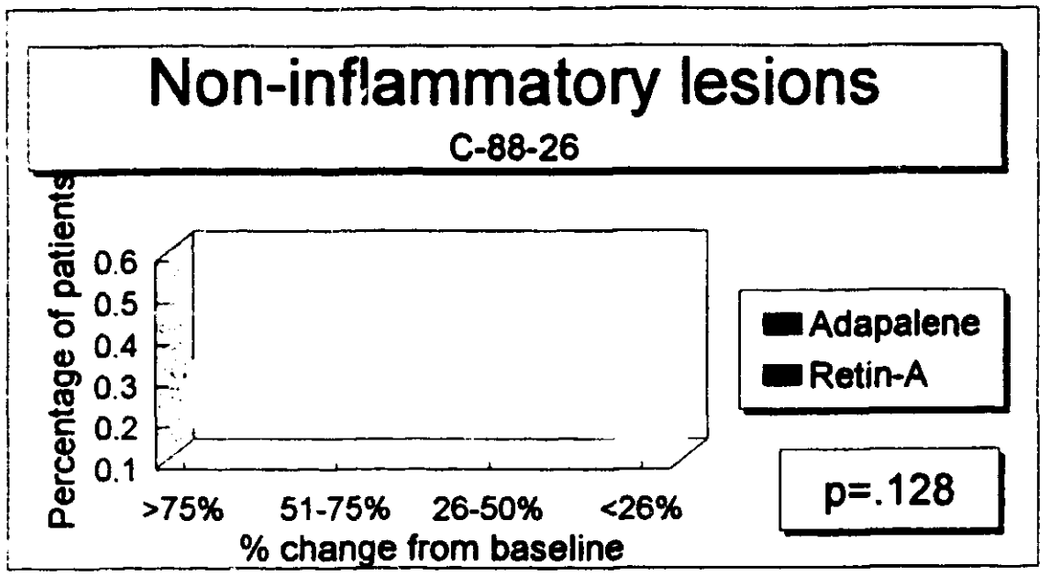

Non-inflammatory lesions
9104-CD271L-EV
Percentage of patients
0.6
0.4
0.2
0
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Vehicle
p=.02

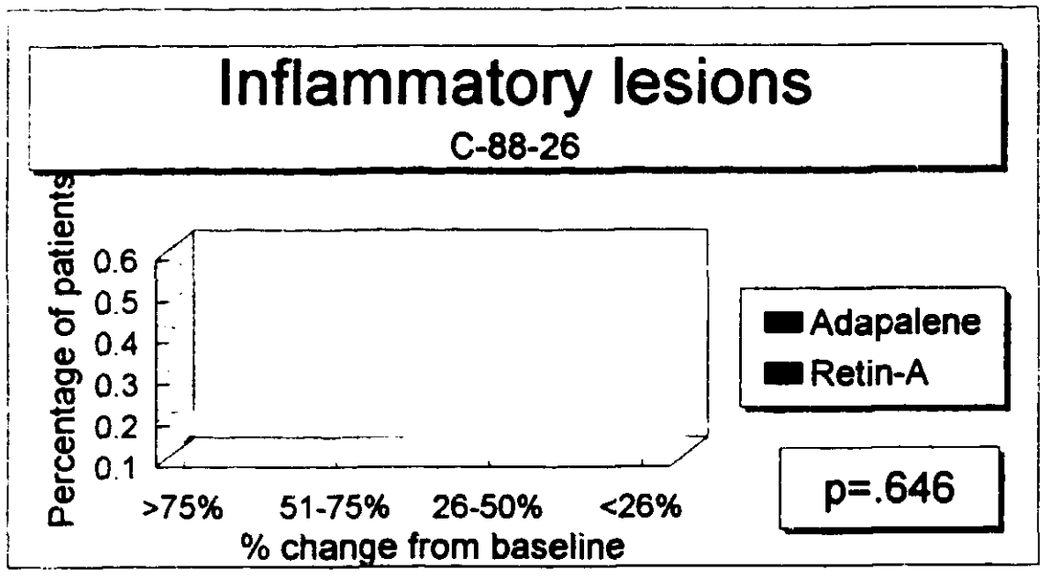

Inflammatory lesions
C-88-27
Percentage of patients
0.6
0.4
0.2
0
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Vehicle
p=.265

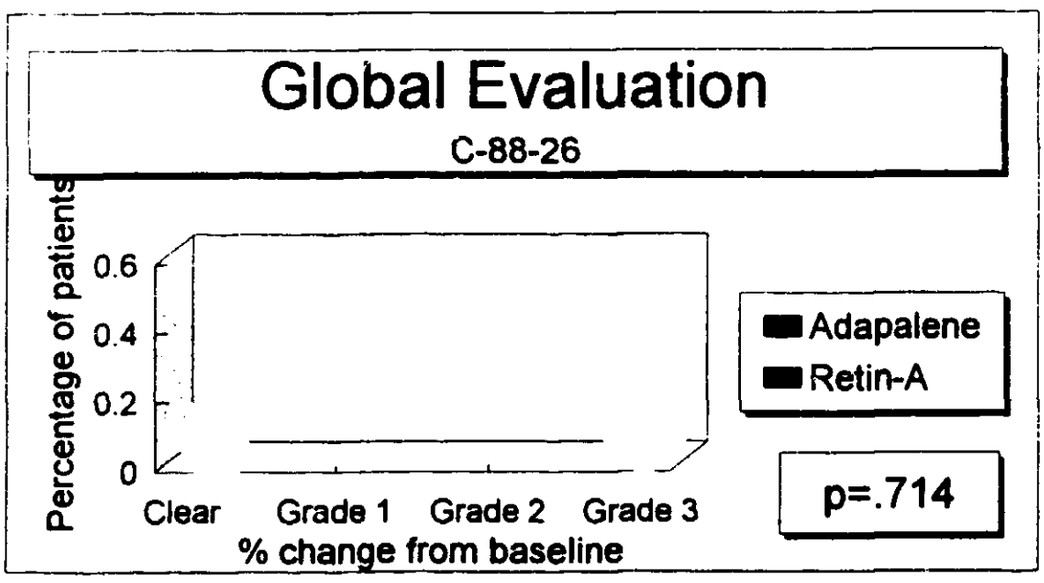

Inflammatory lesions
9104-CD271L-EV
Percentage of patients
0.6
0.4
0.2
0
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Vehicle
p=.177


Global Evaluation
C-88-27
Percentage of patients
0.8
0.6
0.4
0.2
0
Clear
Grade 1
Grade 2
Grade 3
Adapalene
Vehicle
p=.415


Global Evaluation
9104-CD271L-EV
Percentage of patients
0.8
0.6
0.4
0.2
0
Clear
Grade 1
Grade 2
Grade 3
Adapalene
Vehicle
p=.005


Non-inflammatory lesions
C-88-26
Percentage of patients
0.6
0.5
0.4
0.3
0.2
0.1
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Retin-A
p=.128


Inflammatory lesions
C-88-26
Percentage of patients
0.6
0.5
0.4
0.3
0.2
0.1
>75%
51-75%
26-50%
<26%
% change from baseline
Adapalene
Retin-A
p=.646


Global Evaluation
C-88-26
Percentage of patients
0.6
0.4
0.2
0
Clear
Grade 1
Grade 2
Grade 3
% change from baseline
Adapalene
Retin-A
p=.714

Efficacy: (See Statistical Review)

Study Number		Week 12 Lesions- Global- >75% / 51-75% / 26-50% / ≤25% Clear/Grade 1/Grade 2/Grade 3			p Value
		Adapalene	Retin-A	Vehicle	
C-88-27	Non-inflammatory lesions	9/12/11/12		3/15/12/16	**.038**
	Inflammatory lesions	12/11/12/9		7/17/10/12	.265
	Global Grade	0/31/13/0		1/27/16/2	.415
9104-CD271L-EV	Non-inflammatory lesions	13/29/20/33		8/23/20/54	**.020**
	Inflammatory lesions	18/26/21/30		15/25/23/42	.177
	Global Grade	0/36/45/0		0/24/62/5	**.005**
C-88-26	Non-inflammatory lesions	36/28/28/19	22/46/32/26		.128
	Inflammatory lesions	18/46/21/26	23/40/37/26		.646
	Global Grade	0/63/56/1	0/61/63/2		.714

Reviewer's Comments: *The vehicle controlled studies showed a statistically significant effect of Adapalene over vehicle in non-inflammatory lesions in two studies and global effect in one study.*

In addition, there was no statistically significant difference from Retin-A.

Safety

Adverse Event	Adapalene (N=571)	Retin-A (N=281)	Vehicle (N=223)	Results
Skin discomfort (burning and stinging)	21	4	2	Adapalene > Vehicle Adapalene = Retin-A
Skin irritation	14	5	1	Adapalene > Vehicle Adapalene = Retin-A
Erythema	12	2	0	Adapalene > Vehicle Adapalene = Retin-A
Dry skin	11	2	0	Adapalene > Vehicle Adapalene = Retin-A
Pruritus	8	1	3	Adapalene = Vehicle Adapalene = Retin-A

Reviewer's Comments:

Adapalene treated patients had an equivalent percentage of events compared to Retin-A and significantly more events than vehicle.

Labeling:

Reviewer's Comments: *The applicant's latest version of proposed labeling is presented below. Recommended additions are identified by shading and recommended deletions are identified by ~~a single strikeout line.~~*

DIFFERIN™
(adapalene solution)
Solution, 0.1%

DESCRIPTION: DIFFERIN™ Solution, containing adapalene, is used for the topical treatment of acne vulgaris. Each mL of DIFFERIN Solution contains adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol, SD alcohol 40-B, 30% (w/v).

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula:

[structure]

CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Studies in acne patients provide clinical evidence that topical adapalene is effective in reducing the noninflammatory acne lesions.

Pharmacokinetics: Absorption of adapalene through human skin is low. Only trace amounts (<0.25ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.

INDICATIONS AND USAGE: DIFFERIN Solution is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS:

DIFFERIN Solution should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle solution.

WARNINGS: Use of DIFFERIN Solution should be discontinued if hypersensitivity to any of the ingredients is noted. Patients with sunburn should be advised not to use the product until fully recovered.

PRECAUTIONS: ***General***: If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose and mucous membranes. The product should not be applied to cuts, abrasions, or eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of side effects, patients should be instructed to reduce the frequency of application or discontinue use.

Drug Interactions: As DIFFERIN Solution has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol or salicylic acid in combination with DIFFERIN Solution. If these preparations have been used, it is advisable not to start therapy with DIFFERIN Solution until the effects of such preparations on the skin have subsided.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 3, and 10 mg/m²/day (a topical dose in humans is 3 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3, and 9 mg/m²/day). These studies have revealed that the drug was tumorigenic in both species. In the oral studies, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats. In the dermal study, a positive linear trend was observed in the incidence of splenic hemangiosarcomas and hemangiomas. No photocarcinogenicity studies were conducted. However, animals studies have shown an increased tumorigenic risk with the use of similar drugs (e.g., tretinoin) when exposed to UV light in the laboratory or in the sunlight. Patients should avoid or minimize exposure to sunlight. In a series of *in vivo* and *in vitro* studies, adapalene did not demonstrate mutagenic or genotoxic activities.

Pregnancy: Teratogenic effects. Pregnancy Category C.

No teratogenic effects were seen in rats at oral doses of adapalene 0.15-15 mg/kg/day (0.9-90 mg/m²/day), up to 30 times the maximal daily human topical dose (mg/m²/day). Dermal teratology studies conducted in rats and rabbits at 4-8 times (mg/m²/day) the human dose exhibited no fetotoxicity in rabbits 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.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

Some degree of adverse effects such as erythema, scaling, dryness, pruritus and burning will occur in 30-60% of patients. Pruritus or burning immediately after application also occurs in approximately 30% of patients. The following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, sunburn and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN Solution during clinical trials were reversible upon discontinuation of therapy.

OVERDOSAGE: DIFFERIN Solution is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur. The acute oral toxicity of DIFFERIN Solution in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: DIFFERIN Solution should be applied once a day to affected areas after washing in the evening before retiring A thin film of the solution should be applied, avoiding eyes, lips and mucous membranes.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

Patients should be advised to use non-comedogenic cosmetics.

HOW SUPPLIED: DIFFERIN (adapalene) Solution is supplied in the following sizes:

30 mL glass bottle with applicator - NDC 0299-5905-30
60 mL glass bottle with applicator - NDC 0299-5905-60

The applicator is designed so that the solution may be applied directly to the involved skin.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Keep container tightly closed and store upright.

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:
Galderma Laboratories, Inc.
Fort Worth, Texas 76133 USA

Mfd. by:

DPT Laboratories, Inc.
San Antonio, Texas 78215 USA

GALDERMA is a registered trademark.

Revised: 1996

Reviewer Revised Labeling:

DIFFERIN™ (adapalene solution)
Solution, 0.1%

DESCRIPTION: DIFFERIN™ Solution, containing adapalene, is used for the topical treatment of acne vulgaris. Each mL of DIFFERIN Solution contains adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol, SD alcohol 40-B, 30% (w/v).

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula:

[structure]

CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Studies in acne patients provide clinical evidence that topical adapalene is effective in reducing the noninflammatory acne lesions.

Pharmacokinetics: Absorption of adapalene through human skin is low. Only trace amounts (<0.25ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.

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Avoid contact with the eyes, lips, angles of the nose and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of side effects, patients should be instructed to reduce the frequency of application or discontinue use.

Drug Interactions: As DIFFERIN Solution has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol or salicylic acid in combination with DIFFERIN Solution. If these preparations have been used, it is advisable not to start therapy with DIFFERIN Solution until the effects of such preparations on the skin have subsided.

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Pregnancy: Teratogenic effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15-15 mg/kg/day (0.9-90 mg/m^2/day), up to 30 times the maximal daily human topical dose (mg/m^2/day). Dermal teratology studies conducted in rats and rabbits at 4-8 times (mg/m^2/day) the human dose exhibited no fetotoxicity in rabbits 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.

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DOSAGE AND ADMINISTRATION: DIFFERIN Solution should be applied once a day to affected areas after washing in the evening before retiring. A thin film of the solution should be applied, avoiding eyes, lips and mucous membranes.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

Patients should be advised to use non-comedogenic cosmetics.

HOW SUPPLIED: DIFFERIN (adapalene) Solution is supplied in the following sizes:

30 mL glass bottle with applicator - NDC 0299-5905-30
60 mL glass bottle with applicator - NDC 0299-5905-60

The applicator is designed so that the solution may be applied directly to the involved skin.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Keep container tightly closed and store upright.

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:
Galderma Laboratories, Inc.
Fort Worth, Texas 76133 USA

Mfd. by:

DPT Laboratories, Inc.
San Antonio, Texas 78215 USA

GALDERMA is a registered trademark.

Revised: 1996

Recommendations

NDA 20-338, Differin (adapalene solution), 0.1% is recommended for approval with labeling revisions as identified in this review.

Wiley A. Chambers MD
Wiley A. Chambers, M.D.
Clinical Team Leader

5/31/96

cc: HFD-540
HFD-340
HFD-540/PM/Kozma-Fornaro
HFD-520/CHEM/Timper
HFD-540/PHARM/Mainigi
HFD-540/MO/Toombs
HFD-550/ActgDivDir/Chambers
HFD-713/STAT/Srinivasan

MAY 31 1996

Clinical Team Leader Review of NDA 20-338
Review #3

NDA 20-338
Review #3

Submission dated: 5/30/96
Review completed: 5/31/96

Drug name: Differin Solution, 0.1%
Generic name: Adapalene solution

Sponsor: Owen/Galderma Laboratories, Inc.
Fort Worth, TX 76115

Pharmacologic Category: Retinoid

Proposed Indication(s): Treatment of acne vulgaris

Related Reviews:

Clinical Review dated	10/ 7/93
Clinical Addendum dated	3/30/94
Supervisory MOR dated	7/ 5/94
Statistical Review dated	11/ 9/93
Clinical Team Leader review dated	4/12/96

Background:

There is an inconsistency between the results as reported in the clinical review and the statistical review. The difference is related to the method of analysis performed. The Supervisory MOR dated 7/5/94 was based on the original MOR. After re-review of that data in conjunction with the statistical review, a determination was made that the more appropriate analysis for these trials is the one performed by the FDA statistical review team.

Efficacy: (See Statistical Review)

Study Number		Week 12 Lesions- Global- >75% / 51-75% / 26-50% / ≤25% Clear/Grade 1/Grade 2/Grade 3			p Value
		Adapalene	Retin-A	Vehicle	
C-88-27	Non-inflammatory lesions	9/12/11/12		3/15/12/16	**.038**
	Inflammatory lesions	12/11/12/9		7/17/10/12	.265
	Global Grade	0/31/13/0		1/27/16/2	.415
9104-CD271L-EV	Non-inflammatory lesions	13/29/20/33		8/23/20/54	**.020**
	Inflammatory lesions	18/26/21/30		15/25/23/42	.177
	Global Grade	0/36/45/0		0/24/62/5	**.005**
C-88-26	Non-inflammatory lesions	36/28/28/19	22/46/32/26		.128
	Inflammatory lesions	18/46/21/26	23/40/37/26		.646
	Global Grade	0/63/56/1	0/61/63/2		.714

Reviewer's Comments: *The vehicle controlled studies showed a statistically significant effect of Adapalene over vehicle in non-inflammatory lesions in two studies and global effect in one study.*

In addition, there was no statistically significant difference from Retin-A.

Safety

Adverse Event	Adapalene (N=571)	Retin-A (N=281)	Vehicle (N=223)	Results
Skin discomfort (burning and stinging)	21	4	2	Adapalene > Vehicle Adapalene = Retin-A
Skin irritation	14	5	1	Adapalene > Vehicle Adapalene = Retin-A
Erythema	12	2	0	Adapalene > Vehicle Adapalene = Retin-A
Dry skin	11	2	0	Adapalene > Vehicle Adapalene = Retin-A
Pruritus	8	1	3	Adapalene = Vehicle Adapalene = Retin-A

Reviewer's Comments:

Adapalene treated patients had an equivalent percentage of events compared to Retin-A and significantly more events than vehicle.

Labeling:

Reviewer's Comments: *The applicant's latest version of proposed labeling is presented below. Recommended additions are identified by shading and recommended deletions are identified by ~~single strikeout line.~~*

DIFFERIN™
(adapalene solution)
Solution, 0.1%

DESCRIPTION: DIFFERIN™ Solution, containing adapalene, is used for the topical treatment of acne vulgaris. Each mL of DIFFERIN Solution contains adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol, SD alcohol 40-B, 30% (w/v).

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula:

[structure]

CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Pharmacokinetics: Absorption of adapalene through human skin is low. Only trace amounts (<0.25ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.

INDICATIONS AND USAGE: DIFFERIN Solution is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: DIFFERIN Solution should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle solution.

WARNINGS: Use of DIFFERIN Solution should be discontinued if hypersensitivity to any of the ingredients is noted. Patients with sunburn should be advised not to use the product until fully recovered.

PRECAUTIONS: ***General***: If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.

Drug Interactions: As DIFFERIN Solution has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol or salicylic acid in combination with DIFFERIN Solution. If these preparations have been used, it is advisable not to start therapy with DIFFERIN Solution until the effects of such preparations in the skin have subsided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4-75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.

No photocarcinogenicity studies were conducted. Animals studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to sunlight or artificial UV irradiation sources.

In a series of *in vivo* and *in vitro* studies, adapalene did not exhibit mutagenic or genotoxic activities.

Pregnancy: Teratogenic effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5 mg/kg/day, up to 120 times the maximal daily human topical dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose 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.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS: Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 30-60% of patients. Pruritus or burning immediately after application also occurs in approximately 30% of patients. The following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN Solution during clinical trials were reversible upon discontinuation of therapy.

OVERDOSAGE: DIFFERIN Solution is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur. The acute oral toxicity of DIFFERIN Solution in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: DIFFERIN Solution should be applied once a day to affected areas after washing in the evening before retiring. A thin film of the solution should be applied, avoiding eyes, lips and mucous membranes.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

HOW SUPPLIED: DIFFERIN (adapalene solution) Solution is supplied in the following sizes:

30 mL glass bottle with applicator - **NDC** 0299-5905-30
60 mL glass bottle with applicator - **NDC** 0299-5905-60

The applicator is designed so that the solution may be applied directly to the involved skin.

Storage: Store at controlled room temperature 20°-25°C (68°-77°F). Keep container tightly closed and store upright.

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:
Galderma Laboratories, Inc.
Fort Worth, Texas 76133 USA

Mfd. by:

DPT Laboratories, Inc.
San Antonio, Texas 78215 USA

GALDERMA is a registered trademark.

Revised: May 1996

Recommendations

NDA 20-338, Differin (adapalene solution), 0.1% is recommended for approval with the labeling submitted May 30, 1996.

Wiley A. Chambers, M.D.
Clinical Team Leader

5/31/96

cc: HFD-540
HFD-340
HFD-540/PM/Kozma-Fornaro
HFD-520/CHEM/Timper
HFD-540/PHARM/Mainigi
HFD-540/MO/Toombs
HFD-550/ActgDivDir/Chambers
HFD-713/STAT/Srinivasan

Clinical Team Leader Review of NDA 20-380
Review #4

MAY 3 1 1996

NDA 20-380
Review #4

Submission dates: 5/16/96 and 5/30/96
Review completed: 5/31/96

Drug name: Differin Gel, 0.1%
Generic name: Adapalene gel

Sponsor: Owen/Galderma Laboratories, Inc.
Fort Worth, TX 76115

Pharmacologic Category: Retinoid

Proposed Indication(s): Treatment of acne vulgaris

Related Reviews:

Clinical Review dated	4/ 5/94
Supervisory MOR dated	7/20/94
Supervisory MOR dated	11/ 9/94
Biopharmaceutics Review dated	3/ 7/94
Statistical Review dated	4/21/94
Team Leader MOR dated	4/12/96

Background:

There is an inconsistency between the results as reported in the clinical review and the statistical review. The difference is related to the method of analysis performed. The Supervisory MOR dated 7/5/94 was based on the original MOR. After re-review of that data in conjunction with the statistical review, a determination was made that the more appropriate analysis for these trials is the one performed by the FDA statistical review team.

Efficacy: (See Statistical Review)

Study Number		Week 12 % Reduction from baseline			
		Adapalene 0.1%	Retin-A 0.025%	Vehicle	p Value or 95% Conf Interval
C-89-61	Non-inflammatory lesions	**48%**	39%	35%	**.059**
	Inflammatory lesions	**46%**	44%	36%	.138
9105-CD271G-EV	Non-inflammatory lesions	26%		1%	**.001**
	Inflammatory lesions	34%		12%	**.01**
	Global Grade	1.21		1.34	**.058**
CR88091	Non-inflammatory lesions	73%	**81%**		-18,2
	Inflammatory lesions	65%	**71%**		-20,9
	Global Grade	**77%**	74%		-8,14
CR89064	Non-inflammatory lesions	63%	**64%**		-1,1
	Inflammatory lesions	55%	**60%**		-16,6
	Global Grade	54%	**57%**		-11,6
CR 89-32	Non-inflammatory lesions	**46%**	33%		**.2,26**
	Inflammatory lesions	**48%**	38%		-2,22

Reviewer's Comments: *The vehicle controlled studies showed a significant effect of Adapalene over vehicle in non-inflammatory lesions in both studies (marginally in one) and a significant effect in the global evaluation in one study.*

In the comparison studies to Retin-A 0.025%, the effects were clinically equivalent in each group.

Labeling:

Reviewer's Comments: *The applicant's latest version of proposed labeling is presented below. Recommended additions are identified by shading and recommended deletions are identified by ~~single strikeout line.~~*

DIFFERIN™
(adapalene gel)
Gel, 0.1%

DESCRIPTION: DIFFERIN™ Gel, containing adapalene, is used for the topical treatment of acne vulgaris. Each gram of DIFFERIN Gel contains adapalene 0.1% (1 mg) in a vehicle consisting of propylene glycol, carbomer 940, poloxamer 182, edetate disodium, methylparaben, sodium hydroxide, and purified water. May contain hydrochloric acid to adjust pH.

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula:

[structure]

CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Pharmacokinetics: Absorption of adapalene through human skin is low. Only trace amounts (<0.25ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.

INDICATIONS AND USAGE: DIFFERIN Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: DIFFERIN Gel should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle gel.

WARNINGS: Use of DIFFERIN Gel should be discontinued if hypersensitivity to any of the ingredients is noted. Patients with sunburn should be advised not to use the product until fully recovered.

PRECAUTIONS: *General*: If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.

Drug Interactions: As DIFFERIN Gel has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol or salicylic acid in combination with DIFFERIN Gel. If these preparations have been used, it is advisable not to start therapy with DIFFERIN Gel until the effects of such preparations in the skin have subsided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4-75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.

No photocarcinogenicity studies were conducted. Animals studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to sunlight or artificial UV irradiation sources.

In a series of *in vivo* and *in vitro* studies, adapalene did not exhibit mutagenic or genotoxic activities.

Pregnancy: Teratogenic effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5 mg/kg/day, up to 120 times the maximal daily human topical dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose 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.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Gel is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS: Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients. Pruritus or burning immediately after application also occurs in approximately 20% of patients. The following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN Gel during clinical trials were reversible upon discontinuation of therapy.

OVERDOSAGE: DIFFERIN Gel is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur. The acute oral toxicity of DIFFERIN Gel in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: DIFFERIN Gel should be applied once a day to affected areas after washing in the evening before retiring. A thin film of the gel should be applied, avoiding eyes, lips and mucous membranes.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

HOW SUPPLIED: DIFFERIN (adapalene gel) Gel 0.1% is supplied in the following sizes:

15 g laminate tube - NDC 0299-5910-15
45 g laminate tube - NDC 0299-5910-45

Storage: Store at controlled room temperature 20°-25°C (68°-77°F).

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:
Galderma Laboratories, Inc.
Fort Worth, Texas 76133 USA

Mfd. by:
DPT Laboratories, Inc.
San Antonio, Texas 78215 USA

GALDERMA is a registered trademark.

Revised: May 1996

Recommendations

NDA ~~20-338~~ 20-380, Differin (adapalene gel), 0.1% is recommended for approval with labeling submitted on May 30, 1996.

Wiley A. Chambers, M.D.
Clinical Team Leader

5/31/96

cc: HFD-540
HFD-340
HFD-540/PM/Kozma-Fornaro
HFD-540/CHEM/DeCamp
HFD-540/PHARM/Mainigi
HFD-540/MO/Toombs
HFD-520/CLIN REV/Bostwick
HFD-550/ActgDivDir/Chambers
HFD-713/STAT/Chakravarty

ADAPALENE SOLUTION, 0.1%

4-MONTH SAFETY UPDATE TO NDA

TABLE OF CONTENTS

A. INTRODUCTION

An NDA on adapalene solution was submitted to the FDA in March of 1993. Although the NDA was specific for adapalene solution, there are a total of three dosage forms of adapalene being evaluated (solution, gel and cream). Each formulation has been studied under a separate IND. This four month safety update for NDA 20-338 includes information on the three dosage forms of adapalene. The table below outlines the status of submissions and numbers of humans exposed to each formulation.

		NUMBER EXPOSED	
Dosage Form	Status	Healthy Volunteers	Acne Patients
Solution, 0.1%	NDA submitted (20-338)	199	571
	New Clinical Experience	None	None
Aqueous Gel, 0.1%	NDA submitted (20-380)	271	661
	New Clinical Experience	74	86
Cream, 0.1%	Clinical trials completed- results being analyzed. NDA targeted for 1994.	25	175 (U.S.) 139 (European)
TOTAL:		569	1632 = **2201**

Since the filing of NDA 20-338, no humans have been exposed to adapalene solution. Exposure to adapalene, however, has increased due to the studies conducted with the aqueous gel and cream formulations. The labeling for adapalene solution has not been altered or revised by this increase in human exposure. In fact, adverse events are less frequent with both the aqueous gel and cream dosage forms (refer to Table 1).

B. UPDATE OF PRECLINICAL INFORMATION

1. Adapalene Solution

There have been no new preclinical toxicology studies performed on adapalene solution since the filing of NDA 20-338.

2. Adapalene Gel

There have been no new preclinical toxicology studies on adapalene aqueous gel since the filing of NDA 20-380.

3. Adapalene Cream

There have been no new preclinical toxicology studies performed on adapalene cream since the filing of IND

C. UPDATE OF CLINICAL INFORMATION:

1. Adapalene Solution

There have been no new clinical (Phase I or II) trials performed on adapalene solution since the filing of NDA 20-338.

2. Adapalene Gel

Four pharmacology studies in healthy volunteers and one clinical trial in acne patients have been completed since the filing of NDA 20-380 for adapalene gel. Refer to Table 2 for an overview of these studies.

The pharmacology studies revealed no new information about adapalene. There was no evidence of cumulative irritation when used in conjunction with other anti-acne products, and no phototoxicity or photoallergy potential. The Phase II clinical trial (CR92142) in acne patients has been completed and the data is being analyzed. There were no serious treatment related medical events reported.

A human pharmacokinetic study was conducted with the aqueous gel formulation which provides relevant data on absorption and excretion of adapalene from topical application. The percutaneous absorption study (CR90103) showed that under conditions resembling maximum exposure to adapalene gel 0.1% in the therapy of acne, (2g/day) absorption did occur as confirmed by the low quantities of parent substance eliminated in the feces, but that this was not, in general, associated with detectable levels of circulating adapalene. A summary of this study is attached. The complete report can be found in adapalene gel NDA 20-380.

3. Adapalene Cream

Two clinical trials have been completed on the adapalene cream 0.1% dosage form since the filing of NDA 20-338. Once again, the safety profile and product labeling of adapalene solution is not affected.

A total of 175 patients were studied in the U.S. and 139 patients were studied in Europe. Both of the clinical trials were similar in design with the exception of the concurrent control. The U.S. study incorporated a vehicle controlled design (adapalene cream 0.1% vs. vehicle) and the European study was a reference-controlled trial (adapalene cream 0.1% vs. Retin-A Cream 0.05%).

Although the medical events were similar in intensity and duration during both of the multi-clinic trials, the incidence rates were less with the cream formulation than those reported with the adapalene solution.

None of the patients were discontinued due to a serious treatment related event.

D. LITERATURE UPDATE

There have been no new published reports concerning adapalene (solution, gel or cream.)

E. CONCLUSION

A total of 2201 healthy volunteers and acne patients have been exposed to adapalene in a solution, gel or cream dosage form. There have been no serious treatment related medical events reported in any of these studies. The medical events reported for the three dosage forms of adapalene were similar in type, intensity and duration, but slightly less in frequency for the gel and cream forms than for the solution. This may be attributed to the alcoholic content in the solution vehicle. No new information has been collected which would affect the safety profile or the product labeling for adapalene solution 0.1%.

F. TABLES AND ATTACHMENTS

TABLE 1
FREQUENCY AND INCIDENCE OF MEDICAL EVENTS

	Adapalene Solution N=571			Adapalene Gel N=661			Adapalene Cream N=314(a)		
Medical Events (Dermatologic)	# of ME's	# of Patients	Incid. %	# of ME's	# of Patients	Incid. %	# of ME's	# of Patients	Incid. %
RELATED	N	N	%	N	N	%	N	N	%
Skin Discomfort	21	21	(3.7)	4	4	(0.6)	1	1	(0.3)
Skin Irritation	14	14	(2.4)	4	4	(0.6)	5	5	(1.6)
Erythema	12	12	(2.1)	6	6	(0.9)	1	1	(0.3)
Skin Dry	11	11	(1.9)	7	7	(1.1)	1	1	(0.3)
Pruritus	8	8	(1.4)	2	2	(0.3)	0	0	-
Dermatitis	3	3	(0.5)	1	1	(0.2)	0	0	-
Sunburn	2	2	(0.3)	1	1	(0.2)	0	0	-
Acne (Flare)	1	1	(0.2)	3	3	(0.5)	2	2	(0.6)
Impetigo (Flare)	1	1	(0.2)	0	0	-	0	0	-
Edema (Eyelid)	0	0	-	0	0	-	2	2	(0.6)
POSSIBLY RELATED									
Sunburn	8	7	(1.2)	2	2	(0.3)	3	3	(0.9)
Dermatitis	2	2	(0.3)	1	1	(0.2)	0	0	-
Contact Dermatitis	0	0	-	1	1	(0.2)	2	2	(0.6)
Acne (Flare)	1	1	(0.2)	2	2	(0.3)	0	0	-
Pruritus	0	0	-	1	1	(0.2)	0	0	-
Skin Discomfort	0	0	-	1	1	(0.2)	0	0	-
Erythema	0	0	-	1	1	(0.2)	0	0	-
Vesicular Rash	0	0	-	1	1	(0.2)	0	0	-
Cyst (face)	0	0	-	1	1	(0.2)	0	0	-
Herpes Simplex	0	0	-	1	1	(0.2)	0	0	-

(a) Excluded patients (86) from CR92143 since medical events have not been tabulated.

TABLE 2
OVERVIEW OF STUDIES WITH ADAPALENE GEL
WHICH WERE COMPLETED SINCE SUBMISSION OF NDA 20-380

Study No.	Description	Treatment(s)	No. of Subjects *	Treatment Duration
CR 92144	Cumulative Skin Irritation	Combination of Adapalene gel with each of the following: benzoyl peroxide, clindamycin phosphate or erythromycin	25	3 weeks
CR 92140	Cumulative Skin Irritation	Adapalene gel Adapalene gel (different preservative)	25	3 weeks
CR 92143	Phototoxicity Potential	Adapalene gel Tretinoin gel Isotretinoin gel Adapalene gel vehicle	12	1 day
CR 92141	Photo-irritation Potential	Adapalene gel Tretinoin gel	12	15 days
CR 92142	Safety and Efficacy (acne patients)	Adapalene gel Isotretinoin gel	86	12 weeks

*Exposed to Adapalene Gel

ATTACHMENT 1
STUDY CR90103 SUMMARY REPORT

STUDY REPORT CR 90103

INVESTIGATION OF THE PHARMACOKINETIC AND METABOLIC PROFILE OF CD 271 FOLLOWING A 14-DAY APPLICATION OF THE PRODUCT IN A GEL FORMULATION IN HUMAN ACNE PATIENTS

APPROVALS :

/23/02/93/
Dr M. VERSCHOORE
Study Investigator

/19/02/93/
D. CARON
Experimentator, Trial Manager

/19/02/93/
P. BUCHAN
Monitor

/19/02/93
Pr. J.P.ORTONNE
C.P.C.A.D. Director

COLLABORATION :

J.C. CARON / C. D'AUTHIER / C. VERRIER

DISTRIBUTION :

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. To the persons above (M. VERSCHOORE, D. CARON, P. BUCHAN, J.P. ORTONNE)
. Sponsor CIRD GALDERMA : J.P. BILLOT (abstract only)

STUDY REPORT CR 90103

INVESTIGATION OF THE PHARMACOKINETIC AND METABOLIC PROFILE OF CD 271 FOLLOWING A 14-DAY APPLICATION OF THE PRODUCT IN A GEL FORMULATION IN HUMAN ACNE PATIENTS

SUMMARY

This study was designed to investigate the pharmacokinetic behaviour of adapalene under conditions resembling as closely as possible the maximum exposure likely to be encountered in the treatment of acne. The study was conducted in six Caucasian subjects with acneic lesions, three males (nos 1, 3 & 4) aged 27 to 33 years, weighing 70 to 90 kg and three females (nos 2, 5 & 6) aged 24 to 36 years, weighing 50 to 53 kg. The test article, an aqueous gel suspension containing 0.1 % adapalene, was applied at a target dose of 2 g formulation (=2 mg adapalene) each morning from day 1 to day 14 to the face, shoulders and chest (corresponding to an area of approximately 1000 cm^2) by the subjects themselves under supervision.

Blood samples were taken prior to the first application, at 12-hour intervals on days 2, 3, 4, 5, 14 & 15 and once daily on days 1, 8, 11, 17, 21 & 28. Urine samples were collected over 24-hour intervals just prior to, and throughout the treatment period. Faecal samples were collected over 24-hour intervals just prior to, throughout treatment, and for a further 14 days following treatment. Samples of stratum corneum were obtained by serially stripping fifteen times with adhesive tape three different zones of 5.7 cm^2 on the shoulders at 24 hours, 7 & 14 days after the last administration of test article. Strips of stratum corneum taken from a non-treated zone of the back served as controls. The adapalene content of all samples was measured using an HPLC method with fluorescence detection. All samples except the stratum corneum strippings were subjected to enzymatic hydrolysis prior to analysis so that total (free plus conjugated) adapalene levels could be measured.

As a result of facial cutaneous reactions, subjects 1, 5 & 6 discontinued application of the test article to the face (subject 1 on days 8, 9 and 14, subject 5 from day 9 to 12, and subject 6 from day 9 to 13). However, the daily target dose was maintained by applying the total dose to the chest and shoulders where the test article was well-tolerated. Subjects 2, 3 & 4 continued application to the face throughout the treatment period.

The levels of adapalene in the tape-stripped samples of stratum corneum taken 24 hours after the last application ranged from 31 to 371 $ng.cm^{-2}$ (mean 186 +/- 142 $ng.cm^{-2}$) whereas no quantifiable levels ($\leq$ 25 ng per pool of five strips) were found in samples taken at 7 & 14 days after the last application.

Plasma levels of adapalene were below the limit of detection (0.15 ng. mL^{-1}) in all samples with the exception of a value of 0.38 $ng.mL^{-1}$ in subject 2 on day 3 and trace levels (0.15 - 0.25 $ng.mL^{-1}$) in subject 2 on day 14 and subject 5 on day 2.

The levels of adapalene in urine were below the limit of detection (0.02 $ng.mL^{-1}$) in all samples with the exception of values of 0.08 & 0.06 $ng.mL^{-1}$ found in day 11/12 samples of subjects 2 & 5 respectively and trace levels (0.02 - 0.05 $ng.mL^{-1}$) in the day 2/3 sample from subject 5 and the day 8/9 sample from subject 6.

Adapalene was first detected in day 2/3 faecal samples and was present in all but four of the subsequent faecal samples collected during the treatment period. The faecal levels of adapalene declined after stopping treatment with the last detectable levels (≥ 4 ng.g^{-1} of dry faeces) being recorded in the day 19/20 samples. Within-subject variations in the daily elimination of adapalene were observed which was not surprising in view of irregularity in timing and degree of defaecation. However, pronounced differences between individuals could clearly be discerned, with the cumulative quantities of adapalene measured in faecal samples collected during and after treatment ranging from 0.89 to 15.40 µg (mean 6.77 +/- 6.18 µg).The faecal elimination rate of adapalene reached a maximum of about 2 µg per day in the two subjects, 3 & 4, with the highest cumulative elimination. A positive correlation was observed between the adapalene content and the weight of faecal samples collected from day 2 to the end of the treatment period both on a between-subject and within-subject basis. A possible explanation for this observation is that a greater faecal weight may be associated with a more efficient intestinal transit which interrupts the enterohepatic circulation of adapalene, thus reducing further metabolism.

These results show that under conditions resembling maximum exposure to adapalene gel in the therapy of acne absorption did occur as confirmed by the low quantities of parent substance eliminated in the faeces, but that this was not, in general, associated with detectable levels of circulating adapalene. However, as no account is taken of the potential metabolic transformation of adapalene, the faecal levels of parent substance cannot be used to estimate its absolute absorption.

PATENT AND EXCLUSIVITY INFORMATION

1. **Active Ingredient:** ADAPALENE

2. **Strength:** 0.1% (1 mg/mL)

3. **Trade Name:** DIFFERIN™

4. **Dosage Form, Route of Administration:** Topical Solution

5. **Applicant Firm Name:** Owen/Galderma Laboratories, Inc.

6. **Exclusivity:** The applicant requests 5 years exclusivity for the drug product subsequent to approval of this new drug application.

7.

Applicable Patent Number(s)	Expiration Date	Patent Holder
4,717,720	January 5, 2005	C.I.R.D.*

8. **Brief description of each patent which claims the drug:**

4,717,720 - claims the compound 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid, ADAPALENE, and its use in effective amounts in pharmaceutical compositions suitable for internal, topical, parenteral or ocular administration.

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*

GENERIC DRUG ENFORCEMENT ACT OF 1992

CERTIFICATION STATEMENT

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and pursuant to the July 27, 1992 letter from Jane E. Henney, M.D., FDA Deputy Commissioner for Operations, the applicant makes the following statement in connection with this New Drug Application for DIFFERIN™ (Adapalene) Topical Solution, 0.1%

This is to certify that, to the best of our knowledge, the applicant, Owen/Galderma Laboratories, Inc., did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306 (a) or (b)] in connection with this New Drug Application.

December 14, 1992
(Date)

Christine E. Shank
(Signature)

Christine E. Shank
Manager, Regulatory Affairs
Owen/Galderma Laboratories, Inc.

EXCLUSIVITY SUMMARY for NDA # 20338 **SUPPL #** _____

Trade Name Differin **Generic Name** adapalene solution

Applicant Name Galderma **HFD-** 540

Approval Date _____ 1995

PART I **IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product. NA

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III. ✓

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Mary-Jean Hopma Turner
Signature
Title: Project Manager

12/6/95
Date

Signature of Division Director

5/31/96
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20338 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 AP

HFD 540 Trade (generic) name/dosage form: Differin (adapalene solution) Solution, 0.1%

Applicant Galderma Therapeutic Class Retinoid

Action: AP AE NA

Indication(s) previously approved none

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Acne vulgaris

(For supplements, answer the following questions in relation to the proposed indication.)

✓ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required. — Indicated for ages 12 and up. - spr

Further studies will be done if use for use 12 + below is pursued.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Mary Jean Kyma Lanew
Signature of Preparer and Title (PM, CSO, MO, other)

5/31/96
Date

cc: Orig NDA/PLA # 20338
HFD 540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

Pharm

Review And Evaluation Of Pharmacology And Toxicology Data
Division Of Anti-Infective Drug Products, HFD-520

NDA: 20-338 (Original submission dated 3-29-1993)

Drug: Differin™ Solution, 0.1% (Adapalene Topical Solution)

Sponsor: Owen/Galderma Laboratories, Inc.
6201 South Freeway
P.O Box 6600 Fort Worth, Tx. 76115
817-293-0450

Number of volumes: 68 (sixty-eight)

Date CDER Received: 3-29-1993

Date Assigned: 7-27-1993

Date Review Started: 9-8-1993

Date 1st Draft Completed: 12/28/93

Date Review Accepted by Supervisor: 6/13/94

Dosage and Route of Administration: Topical solution, 0.1% (1mg/mL)

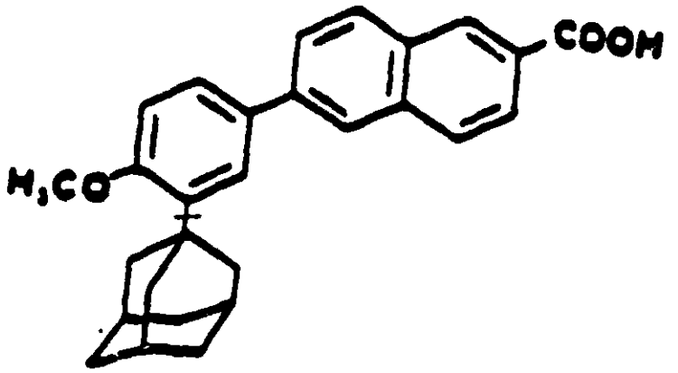
Category: Naphthoic acid class anti-acne agent

Indication: Treatment of acne vulgaris

Review Objectives: To evaluate the preclinical safety of the proposed drug to get approval for marketing in the United States.

Chemical Names: 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

Other Names: Adapalene (USAN); Code names - CD 271; ALϕ2866



Index Of Studies

BIODISPOSITION

1. Extended ADME study in rats.
2. Tissue distribution in rats.
3. Drug release following a single topical application of three formulations in man.
4. Metabolic profile in man after topical application.
5. Plasma kinetics in dog, rat, and rabbit.
6. Interspecies metabolic studies in hepatocyte culture.
7. *In vitro* liberation penetration in human dermatomized skin.
8. Plasma protein binding.

Toxicokinetics

9. Six-week cutaneous toxicity study in rabbit.
10. Three-month percutaneous toxicity study in rabbit.
11. Six month dermal toxicity study in rabbit.
12. Twenty-six weeks oral (gavage) toxicity study in rat.
13. Thirteen-week dietary toxicity study in rat.
14. Thirteen-week dietary toxicity study in rat followed by a four week recovery period.
15. Four-week oral toxicity study in dog.

Oncogenicity

16. Oral oncogenicity/chronic toxicity study in rats (I).
17. Oral oncogenicity/chronic toxicity study in rats (II).
18. Topical oncogenicity study in mice.

Note: A number of animal studies supporting the preclinical safety of this drug were reviewed under INDS

Test substance: ^{14}C-CD-271, specific activity 192.7 µCi/100 ug, radiochemical purity 97%.

Solvent: % NaCl solution.

Animals received intravenous doses of 0.5mg/100 gbw CD 271 (2.5 mL/100g bw) via the tail vein. Three rats/sex were marked for separate collection of urine and feces. These samples were collected at 0-6, 6-24, 24-48, 48-72, 72-96,96-120, 120-144, and 144-168 hours post dose. After collection of blood samples, rats were sacrificed and the following tissues/body fluids were collected:

Adrenals	Ovaries/testes
Gastro-intestinal tract and contents	Plasma
Kidney	Perirenal fat
Liver	Spleen, subcutaneous fat
Mammary tissue	Uterus
	Remaining carcass

The amount of radioactivity was determined in all samples of urine, feces, cage wash, tissues and body fluids.

At 312 hours post-dose feces and urine samples (312-336h) were collected from another group of 3 rats/sex. After that rats were sacrificed and tissues/body fluids collected as before.

The same procedure was repeated at 648 and 1320 post-dose hours with second and third sets of 3 rats/sex.

Results/Conclusions

The radioactivity widely distributed in the body was mainly excreted in the feces (M= 91.5%, F = 87.3% of the administered dose) at 168 hour. Only traces (>1%) were excreted in the urine. At 144 hours post-dose, the amount of radioactivity in the feces was reduced to 0.01% of the administered dose.

At 168 hour, the total radioactivity in tissues and carcasses accounted for a mean average of 3.6 in males and 4.1% in females. The distribution in tissues was as follows:

Radioactivity (ng equiv. g^{-1})

Tissue	Male	Female
Adrenals	362	371
Liver	165	242
Spleen	232	226
Ovaries	-	403

The amount of radioactivity in other tissues was significantly

higher than the detection limit. Mean plasma concentrations at 168 hour ranged from 405 ng equiv. ML^{-1} in both the sexes. The remaining carcass accounted for 1.5-1.9% of the administered dose.

Tissue radioactivity decreased at a very slow rate. At 56 days after dosing, adrenals and ovaries retained significant amounts (289 in males and 346 ng equiv. g^{-1} in females in adrenal; 306 ng equiv. g^{-1} in ovaries) of radioactivity. At this point, approximately 1.5% of the administered dose remained in the body.

2. Commentary on the Tissue Distribution and Elimination Results After I.V. Administration of ^{14}C-CD271 in the Rat in Study Numbers 139705 and 150907 (PB/MCV/92-158; July 1992).

Facility:

Study Objective/Design

Two studies reviewed here investigated the tissue distribution and elimination of i.v. administered radioactivity to Sprague-Dawley rats. The first study in male rats revealed accountable amount of radioactivity present in the tissues at 7 days post-dose. The second study conducted at the same dose level (500 ug/100gbw) in SD rats of both sexes investigated the tissue levels at extended time levels, with sampling time points ranging from 7 to 56 days after dosing. In both studies a common sampling point of 7 days was retained. Two studies were conducted at an interval of 18 months. Two lots (B and C) of ^{14}C-CD 271 were used; the radiochemical purity ranged from 96.5 to 98 percent. The body weights in both studies ranged from 214-253g. Other procedures were essentially similar to study #1 above.

Results/Conclusions

On day 7 in male rats, the tissue levels of total radioactivity in the second study were always higher than in the first study. "The extent to which the tissue levels differed was not consistent, but varied depending on the tissue involved". It was inferred that the differences in tissue distribution resulted form some essential but unknown differences between the two studies.

Table 1 Levels of Tissue Radioactivity (ng equiv/g or mL) Following a Single I.V. Dose (500 ug/100 gbw) of [^{14}c]-CD 271 to Male Rats.

Tissue	Study Number 1 (n=5)	Study Number 2 (n=3)	Increase Factor
Liver	13	165	13
Kidney	6	20	3
Spleen	22	232	11
Adrenals	183	362	2
GI tract	2	12	6

Sub cut. Fat	3	13	4
Testes	4	27	7
Plasma	0.3	5	17

3 Liberation of CD 271 Following a Single Topical Application of 3 Formulations: CF 271/008A, CF 271/172A, CF 271/184 in Human Volunteers (DC/JF/91-141; 1987-1989).

Facility:

Study Objective/Design

In this study the amounts of CD 271 liberated following the applications (50 uL/7.5cm^2) of three formulations all containing 0.1% CD 271, were compared.

Test Formulations:

1. CF271/008A (Lotion)
2. CF271/127A (Gel)
3. CF271/184A (Gel)

Volunteers: 12 persons between 20-42 years age.

Dose Application: Test formulations were applied on the backs for one and 24 hours.

Procedures: After removal of excess drug, the extracts from ten successive strippings of the stratum corneum were assayed by HPLC.

Results

At one hour post application, the amount of adapalene found in the strippings was highest for formulations CF271/184 A (an aqueous gel suspension) and CF 271/172A (an alcoholic gel suspension). The amounts found in both cases accounted for 14% of the dose applied. For CF271/008A (an alcoholic lotion) The amount found was approximately 3 times (4% of the dose applied) lower. At 24 hours, the amounts were as follows:

CF271/184A = 12%
CF271/172 A = 8%
CF271/008 A = 0.4%

4. Investigation of the Pharmacokinetic and Metabolic Profile of CD 271 Following a Single Topical Application of ^{14}C-CD 271 in a Lotion in Human Volunteers (DC/JF/91-142; 1989-1990)

Facility:

Study Objective/Design

In this study, the radioactivity in biological fluids following a single topical application of 0.5 mL of lotion containing 0.1% ^{14}C-CD 271, (CF 271/008A) was determined in 4 male volunteers. Because of very low amounts of radioactivity recovered, the pharmacokinetic parameters and metabolic profile data were not collected.

Sample Collection: Blood samples were collected at 3,6,,12,24,36,48,72,96, and 144 hours and on days 10 and 14 post application.

IRA Project #139705	Intravenous administration of [^{14}C]-CD 271 to male rats (0.5 and 0.05 mg/100g)
IRA Project # 139841	Intravenous administration of [^{14}C]- CD 271 to male rabbits (0.05 mg/100g).

A HPLC method with fluorescence detection for the analysis of CD 271 in plasma was standardized using dog plasma samples spiked with CD 271., The detection limit was established at 0.5mg/100 uL and the limit of reliable determination was considered as 1 ng/100 uL

Results Following the intravenous administration a bi-exponential pattern for CD 271 was obtained in three species. However, after the oral administration in dog, a tri-exponential profile was observed. The values for various pharmacokinetic data (i.v. dose) were as follows:

Half-Life (T1/2) (hrs)	RATS (Two dose) 0.05 mg = 0.4 and 7.4 h 0.5 mg = 0.9 and 13.9h	Rabbits (one dose) 1.05 and 12.4h	Dogs (one dose) 1.4 and 19.2h
Apparent volumes of distribution (Vd) L.$^{-1}$kg^{-1})	4.4 13.4	4.3	1.9
Total body clearance (Cl) L.h^{-1} Kg^{-1})	0.41 0.68	0.24	0.07
AUC (0-inf) ug.h.mL^{-1}	0.121 0.740	2.1	7.4

Urine (24 hour pooled) and feces were collected for a period of 14 days. Gauage dressing, gloves and other articles used for administration and removal of excess lotion were also used to determine total radioactivity.

Results About 94% of the administered radioactivity was found in the excess removed from the surface after 24- hours of application. Only traces of radioactivity were found in the feces of each subject between day 3 and 6. It amounted to about 0.02-0.06% of the administered dose. Some trace amounts were also found in the plasma of 2/4 subjects, however, no significant amount of radioactivity was found in the urine. It was inferred that under the study conditions, absorption was very low.

5. Plasma Kinetics of CD 271 in the Dog, Rat and Rabbit (PB/MCV/92-136; 1989-1992)

Facility:

Study Objective /Design

In these studies the levels of unmetabolized drugs in the plasma were determined by HPLC method. These plasma samples were retained from radiolabeled studies conducted using intravenous or oral administration of [^{14}C] - CD 271 in three species (IRA Project Nos. 139710, 139705, and 139841).

IRA Project # 139710 - Intravenous and oral administration of [^{14}C]-CD 271 to male dogs (0.5mg/and 10mg/100g, respectively).

After the oral administration, the tri-exponential pattern in dog plasma provided the following pharmacokinetic data.

T1/2 for absorption phase = 1.4h
T1/2 for distribution phase = 2.2h
T1/2 for elimination phase = 17.3h
Apparent Vd/F = 42.6h. Kg^{-1}
Clt/F = 1.7 L. h^{-1}
AUC = 5.9 ug.h mL^{-1}
Oral bioavailability F= 0.044

6. Interspecies Metabolic Study of CD -271 in Hepatocyte Culture (CF/JF/92-088; 1991-92).

Facility:

Study Design/Procedures

In this study cultured hepatocytes prepared from male and female rats (241-243g), mice (34-40g), rabbits (3.0-3.1 Kg), human (M=64 years; F=55 years), and male dog (13.5 Kg), were incubated with various concentrations of ^{3}H-CD 271 for various time lengths. The incubated media and in some cases cellular extracts were analyzed for metabolic profiles by HPLC methods. In a few cases intracellular radioactivity was also determined. A number of drug

metabolizing enzymes (phenacetin deethylase, mephenytoin hydroxylase, dextromethorphan demethylase, nitrosoldimethylamine demethylase, and nifedipin oxidase) were determined in microsomal preparations prepared from human liver biopsies. Six enzyme activities (phenacetin deethylase, ethoxyresorufin deethylase, pentoxyresorufin decalkylase, pareacetamol glucuronylsulfotransferase, and procainamide N-acetyl-transferase) were determined in 24-hour human hepatocyte cultures.

Results/Conclusions

Under the assay conditions, drug did not affect the cell morphology. All enzyme activities were within the normal range, except for the mephenytoin hydroxylase activity which was under

Table 1. METABOLISM OF ^{3}H-CD271 (%METABOLIZED) BY CULTURED HEPATOCYTES[a]

INCUBATION	RATS	MICE		RABBIT		MALE DOG		HUMAN	
Time (HRS)	M	F	M	F	M	F		F	M
0	0	0	0	0	0	0	0	0	0
4	0	16.2	4.21	9.3	7.12	0	6.63*	6.63*	11.73
7	8.4	40.96	10.31	26.12	19.2	0	39.54**	39.98**	37.06
24	71.1	93.35	47.20	82.91	77.74	71.08	91.98	91.98	91.58
48	97.4	98.36	81.56	84.1	94.68	95.0	96.99	96.99	98.72

a = Incubation media contained 10^{-7}M ^{3}H-CD271
* Time of incubation 2 hours **Time of incubation 6 hours.

the detection limit in human male. Within 48 hours, almost all the parent drug was metabolized in all the species (Table 1). Taking into account the initial rate of appearance of metabolites in culture media, humans, female rat and mouse were graded as fast metabolisers; both sexes of rabbit exhibited intermediate activities; male rat and mouse were slow metabolisers; and male dog did not metabolize CD-271 till late.

When compared to the culture medium, a high level (17-20 times) of intracellular radioactivity was found in the hepatocytes of all species. The greatest cellular accumulation was observed in male mouse and lowest in human hepatocytes. The major metabolites detected in culture media of all species were M7, M2 and MO/M1, however, in humans and male dog M6 was more prominent than M7. On the other hand, hepatocytes retained parent compound, M6 and M7 for much longer period in their intracellular compartments. Across the species metabolic pattern was similar and no new metabolites were observed in human hepatocytes.

7. Comparison of the In Vitro Liberation-Penetration of CD 271 from Three 0.1% Formulations on Human Dermatotomized Skin (DCa/JF/92-020; June - December 1991).

Facility: Galderma, Valbonne Cedex, France

Study Design

This study was conducted on human dermatotomized skin samples (250 um) obtained from 6 donors. The receptor fluid contained a surfactant. A flow rate/cell with volume ratio equal to 1, was employed during the 15 hours study period.

Formulations Tested:

A. Lotion ^{14}C-524416/R10 (Specific activity, 182.3 uCi/g) CD 271 concentaraion: 0.10%

B. Gel ^{14}C-524635/R12 (Specific activity, 196.6 uCi/g) CD 271 concentration: 0.11%

C. Cream ^{14}C-524827/R11 (Specific activity, 191.8 uCi/g) CD 271 concentration: 0.11%

In each case, 20uL of formulation was applied to 2 cm^2 of skin. Twelve cells were used for each formulation.

Results At the end of the experiment, only traces of radioactivity were detected in the receptor fluid. However, the amount of drug penetrated the skin (dermis and epidermis) was significantly ($p<0.05$) greater with the gel formulation (6.7$\pm$ 4.9%) than with the cream (1.8$\pm$0.9%) or the lotion (1.8$\pm$0.9). Although, no difference was observed in two formulations in the total amount of drug in the skin, the proportion of drug in the dermis compared to the epidermis was observed to be higher (3-4 times; $p<0.05$) for the lotion than for the cream.

8. Investigation of CD271-Plasma Protein Binding by An Erythrocyte Portioning Method (DC/JF/91-143).

Facility:

Study Design In this study, a biological dialysis system involving protein solutions and erythrocytes was used.

Test system Erythrocytes, and plasma were separated from blood samples collected from human volunteers.

Human Proteins: Human serum albumin, α1-acid glycoprotein, gamma-globulins, lipoproteins-VLDL, LDL, and HDL fractions. Stock solutions of these proteins were prepared in phosphate buffer pH 7.4.

^{3}H-CD271: Solution (1.6×10^6dpm/10uL) was prepared in absolute ethanol.

Binding Assay

It is assumed that the free drug in the plasma is in equilibrium with that in the erythrocytes. A uL aliquot of ^{3}H-CD 271 was added to mL of erythrocyte suspension % hematocrit, uL of erythrotets + uL of solution) in protein solution. Samples were incubated at °C for hour, and after centrifugation, aliquots of supernatant were counted for radioactivity. The binding to various proteins and erythrocytes were calculated.

Results Data indicated that in whole blood 26% of CD271 was bound to erythrocytes and the total binding in plasma and blood was greater than 99.3%. The binding constants ($L.g^{-1}$) for various proteins were as follows: human serum albumin-1.28; α-acid glycoprotein-23.6; gamma globulins-0.083, lipoproteins VLDL,-1.2; LDL 14.7, and HDL-13.5.

It was inferred that the extensive blood and plasma binding of drug was primarily due to lipoprotein serum albumin binding, and taking into account the molar concentrations of CD 271 and these proteins, it was unlikely that the drug could be displaced from its binding site in the blood by a competing drug or endogenous substrate.

TOXICOKINETIC MONITORING STUDIES

Note: In most cases only abstracts were provided.

Dermal Studies

9. Six week Cutaneous Toxicity Study with CD 271 Formulated at 0.1 and 0.3% in An Aqueous Gel and 0.3% in a Lotion in the Rabbit. Pharmacokinetic Summary (TX 0481/MD89017; 1988-89).

Facility:

Study Design/Procedures

In this 6- weeks toxicity study, male and female NZW rabbits (2.1-3.0Kg) received daily epidermal applications (2 mL/100g bw) of 0.3% (W/W) aqueous adapalene gel or lotion on 10% of the shaved body surface on the mid-dorsal region. Blood samples were collected 0.5 and 6 hours post-dose on days 2,14, and 28 of treatment and at several time points up to three days after the final application on day 42. Two rabbits/sex were used in this study.

Results

No significant differences in plasma adapalene concentration were observed at any time point of blood collection between the days of treatment and between the two sexes. In addition, similar drug concentrations (24-89 ng/0.1 mL) were observed for the two formulations from days 14 to 42 of treatment. Plasma drug levels decreased slowly after treatment and were still quantifiable at 3 days post-dose.

10. CD 271 Aqueous Gel Suspension: 13-week (3 months) Percutaneous Toxicity Study in the Rabbit. Pharmacokinetic Summary (89 CID 034/0385, 1988-90)

Facility:

Study Design/Procedures

Animals: Male and Female NZW Rabbits (2.6-3.7Kg); 2F+2M/group

Test substance: Aqueous gel suspension and lotion (0.03, 0.1,0.3% w/w).

Dose Level: 0.6,2, and 2.6 mg/100g body weight (2mL/100 gbwt.)

Frequency: Daily.

Respective applications were made on 10-15% of the total body area (15x15cm) between the pectoral and pelvic girdles. Blood samples were collected predose and 6 hours post-dose on days 2, 16, 28, and 42 of treatment and at several time points up to seven days after the last application on day 90.

Results No differences due to sex or formulation were observed in plasma drug levels. The plasma drug concentration did not relate to any time point of sample collection. In all groups, the plasma drug level was lower on day 2 of treatment than any other day of the treatment. Drug concentration declined slowly after the last application with apparent half -lives ranging from 3-6 days.

11. CD 271: Twentysix-week Dermal Studys in the Albino Rabbit. Pharmacokinetic Summary (CDF-46/A; 1989-90).

Facility:

Study Design/Procedures

Animals: Male and female NZW rabbits (2.4-3.2Kg); 5F+5M/group
Test substance: Aqueous gel suspension (0.03, 0.1, 0.3% w/w)

Dose level: Daily

Dermal applications of test gels were made to 10% of the shaved body surface for 26 weeks followed by an 8 week recovery period. Blood samples for determination of plasma drug concentration were drawn after the final dose in week 26 and at the end of the recovery period.

Results
The maximum plasma drug concentrations at three dose levels after 26 weeks of treatment ranged from 9.7 to 21.9 for males and 9.4 to 39.8 ng/100 uL for females. No drug was detected in the untreated controls. Plasma drug concentrations from 1 to 6 ng/mL were considered as trace levels.

ORAL STUDIES

12. CD 271: Toxicity to Rats by Repeated Oral Administration for 26 Weeks with Interim Kill after 13 weeks. Pharmacokinetic Summary (PB/JF/91-130; 1g87-1989).

Facilities:

Study Design

Animals: Male (Average wt. 190g) and female (Average wt.146g). Crl: CD (SD) BR rats; 5F+5M/group.

Test Substance: 0,0.03,0.3, and 3.0 mg/mL CD 271 in 0.5% (W/V) Na Carboxymethylcellulose (5 mL/Kg).

Route: Gavage

Frequency: Daily

Dose Levels: 0,0.15,1.5 and 15mg/kg/day

Results Plasma drug levels at different time points were as follows:

Time	Concentration (ng/mL) Male	FEMALE
HRs		
HRS		
WEEKS hrs)		
WEEKS hrs)		
WEEKS hrs)		

*Controls received drug dose by mistake.

No consistent sex differences in drug plasma levels were detected and no drug accumulation was observed in the plasma at any dose level.

13. CD 271: Toxicity Study by Dietary Administration to CD Rats for 13 Weeks (PB/JF/91-128;1986-1989).

Facility:

Study Design/Procedures

Animals: Male (173-239g) and female (130-190g) CD rats; 5/sex/group

Test substance: 0,5,10 and 20,mg/kg/day CD 271 in powdered diet.

Sample Collection: Blood samples for determination of drug concentrations were drawn at 10, 18,24 hours in weeks 1,6, and 13, however, no blood samples were available from high-dose groups in week 13 due to moribund sacrifices on humane grounds.

Results Cmax (mg/mL) for each time point (10, 18,24 hr) at three dose levels ranged from 31 to 48, from 33 to 52 and from 44 to 63 in males. The corresponding values in females were 29-45, 32-58, and 51-96, respectively. It was inferred that plasma drug levels at any 24 hour period were dose-related, but the relationship was not strictly linear.

14. CD 271: Toxicity Study Dietary Administration to CD Rats for 13 Weeks Followed by a Four Week Reversibility Period (PB/JF/91-129; 1988-1989).

Facility:

Study Design/Procedures

Animals: Male (159-223g) and female (135-184g) CD rats; 5/rats/sex/group.

Test substance

0, 0.15 and 0.15 mg/Kg/day CD 271 in powdered diet.

Blood samples for determination of plasma drug concentration were drawn at 10, 18, and 24 hours in weeks 1, 6, 13 and after 4 weeks of recovery period.

Results Plasma drug levels did not significantly vary with the sampling time but approximately doubled between weeks 1 and 13. Drug levels (range) at different time points were as follows:

Time	Concentration Range (ng/mL)			
	Male		Female	
	LD	HD	LD	HD
Week				
Week				

No drug was detected in plasma samples after 4 weeks of recovery period. Mean plasma concentrations were linear in dose related fashion.

15 CD 271: Oral Dose Range Preliminary Toxicity Study in Dogs by Repeated Oral Administration for 4 Weeks. Pharmacokinetic Summary (PB/JF/91-139; 1987-1988).

Facility:

Study Design: In this exploratory study, male (8.0-9.4kg) and female (7.4-8.3kg) beagle dogs (2/sex/dose group) received daily doses of 10, 30, and 100 mg/Kg CD 271 in gelatine capsules for 4 weeks. Blood samples were drawn at one hour predose and 3 hours post-dose on day 1,15 and 28. Additional samples were collected from high-dose females at 0.5, 1,2,4,6 and 24 hours post-dose on day 28. High dose males were sacrificed for humane reasons before study termination.

Results: Peak drug plasma levels were observed at 3 hours post-dose, however, no significant differences were observed between different days of sampling. No differences in plasma drug levels of males and females were observed.

ONCOGENICITY

16. CD 271: Combined Oncogenicity and Toxicity Study by Dietary Administration to CD Rats for 104 Weeks: Chronic Toxicity Phase (MD/92069; April 1989-Oct 1990)

Facilities: Animal Work.

Analytical Work:

A. **Material And Methods**

1. Test Compound and Diets.

The test compound , CD 271, batch number P059304 was described as a white powder containing % of active ingredient. The individual diets were prepared each week by homogenizing the test compound with the basal rodent diet (Laboratory Animal Diet No. 2). Samples to test homogeneity of CD 271 in the diets were drawn in weeks 1,2,3,4,6,13 and at 13 weeks interval, thereafter. The nominal concentration of test substance in each diet was determined in weeks 1, 2, 3,4, 6,13, 16, 26, 33, 39, 46, 52, 59, 65 70, and 78. Dietary stability of CD 271 was not determined. However, in separate experiments, shelf-life of CD 271 was tested and found to be stable for long term use in the diet.

2. Test Animals: Five To six weeks old male and female CD rats weighing 128 to 272g were used in this study.

B. **Study Design**

1. Animal Assignment: Animals were assigned randomly to the following test groups:

	Test Group	Dose In Diet(ppm)	Main Study 78 weeks		Satellite Study 52 weeks*	
1.	Control	0.00	20	20	10	10
2.	Low-Dose (LD)	0.15	20	20	10	10
3.	MID-Dose (MD)	0.50	20	20	10	10
4.	High-Dose (HD)	1.50	20	20	10	10

* **Control rats were maintained for 104 weeks as veterinary controls.**

2. Dose-Range Finding Studies and Duration of Treatment

Initially, two 13 week (oral) dose-range finding studies were conducted. In the first study, dosages of 5,10, or 20 mg/kg/day were used. Some severe biochemical and morphological changes were observed. It included skeletal abnormalities and excessive osteoclastic and osteoblastic activities indicating active bone remodeling, a familiar phenomenon in rats treated with retinoids. Apparently, none of the dosage was considered suitable for long term administration.

In the second study, oral do es of 0.15 or 0.5 mg/kg/day produced changes in some hematological and biochemical parameters including decreased packed cell volume, Hb concentration, erythrocyte counts and increased plasma levels of alkaline phosphatase and triglycerides. Presumably, these changes are also well associated with retinoids treatment. It was decided to use two tested doses and a dose of 1.5 mg/kg/day (i.e, 10 times the lowest dose) for long-term feeding study.

Drug treated rats in the satellite group used solely for investigations on drug absorption and blood chamistry, were fed for 52 weeks. However, control rats of this group were maintained for 104 weeks as veterinary control. Rats in the main study group were treated for 78 weeks..

The dietary concentrations for adapalene were adjusted weekly for the first 14 weeks of study and biweekly thereafter to maintain the nominal dose values.

C. OBSERVATIONS/DETERMINATIONS

1. Clinical Signs and Mortality

Rats were examined daily for signs of toxicity, morbidity and mortality. More detailed examinations including palpation were conducted every week. Animals judged to be in extremis

were sacrificed. A blood sample was collected prior to each sacrifice.

2. Food Consumption and Body Weights

Body weights were determined weekly during the first 14 weeks of treatment and biweekly thereafter. Food consumption was recorded weekly throughout the treatment period. Food conversion efficiency was determined weekly for the first 14 weeks.

3. Ophthalmoscopy

Indirect ophthalmoscopic examinations were performed on all animals prior to study initiation, and on rats from groups 1 and 4 in weeks 10, 23, 37, 50 and 76.

4. Hematology And Blood Chemistry

Fasting blood samples were drawn from all rats after treatment for 10, 23, 37,50, and 76 weeks. Blood samples obtained from males of groups 3 and 4 were clotted. Similarly, samples obtained after 76 weeks from females of group 2 were clotted. Fasting blood samples were also obtained after 77 weeks from females of groups 1 and 2. Blood samples were used to examine 10 major hematologic and 15 blood chemistry parameters.

5. Urinalysis

Fasting (overnight) urine samples were collected from rats in the main study groups after weeks 11, 24, 37, 50 and 76. Samples were used to evaluate 11 parameters.

6. Absorption

On day 6 and weeks 6, 13,26,39 and 52, blood samples were drawn from all animals of satellite phase. In week 78, blood samples were also drawn from all survivors of main study. Plasma samples were analyzed for drug levels.

7. Gross Pathology And Organ Weights

All survivors, animals killed *in extremis* and found dead during the study were subjected to complete necropsy examination. Major organs (13) were weighed.

8. Histopathology

Thirtyeight tissues/organs from groups 1 and 4 of the main study were subjected to microscopic examinations. In groups 2 and 3, only adrenals, bone, kidneys, liver, spleen and testes were examined. In addition, tissues judged abnormal

during necropsy examination were also examined.

REPORTED RESULTS

1. Clinical Signs and Mortality

No treatment related intergroup differences were observed. The survival rate in week 79 ranged from 15% (HD-females) to 45% (LD-males).

2. Food Consumption and Body Weights

No treatment related intergroup differences were observed. Food conversion efficiency was similar in all groups, and dietary analyses showed that drug levels nearly matched the nominal values.

3. Ophthalmoscopy

No drug related changes were observed.

4. Hematology and Blood Chemistry

At the end of study, packed cell volumes, Hb concentrations and RBC counts in HD males in the main study were significantly (11-13% at $p < 0.05$ to 0.001) lower than the control. In addition; the prothrombin times in HD males were generally shorter than those of controls.

In general, plasma activity of alkaline phosphatase, levels of glucose and triglycerides were significantly increased in high-dose rats. The total plasma protein concentration in all drug treated males were lower than controls throughout the study period. Electrophoretic profiles revealed that these changes were due to low albumin concentrations. The activities of alanine and aspartate amino trasferases were low in all drug treated rats.

5. Urinalysis No treatment related effects were observed.

6. Plasma Drug Level The plasma drug concentrations were increased in a dose related fashion.

7. Gross Pathology and Organ Weights Absolute and relative liver (19%) and adrenal weights (19, 119%) were increased in the high-dose males. Reportedly, changes in adrenal weights were associated with malignant pheochromocytoma. No other drug related macroscopic changes were observed.

8. Histopathology Compared to controls, an increased incidence of benign and malignant pheochromocytoma of adrenals was observed

in the male rats (table 1). Other lesions in the adrenals such as focal nodular hyperplasia (males) and cortical hemorrhagic degeneration (females) indicated that adrenal glands were the primary target of toxicity.

Table 1 Summary of Histopatholical Observations in Rats

Organ/Lesion	Cont	LD	MD	HD	Cont	LD	MD	HD
Adrenal Medulla L & R	20	20	20	20	20	20	20	20
Malignant pheochromocytoma	0	0	0	3	1	0	0	0
Benign pheochromocytoma	2	0	3	5	0	1	0	0
Focal medullary hyperplasia	2	3	1	6	0	0	1	1
Medullary cyst	0	0	1	0	0	0	0	0
Adrenal cortex L & R cortical hemorrhagic degeneration	1	0	0	0	9	11	14	10
Focal cortical hypertrophy	1	1	0	0	0	1	6	1

[a] Number of organs examined are underlined

Diversified, but statistically significant microscopic lesions in other organs were sporadically distributed and therefore, were not considered treatment related.

17. CD 271: Combined Oncogenicity and Toxicity Study by Dietary Administration to CD Rats for 104 Weeks: Oncogenicity Phase (MD/92070/1989-1991.

Facilities:
Drug Lot: P05903

A. **MATERIALS AND METHODS**

1. **Test Compound and Diets**

The individual test diets (0,0.15,0.5, and 1.5mg/Kg) were prepared the same way as in study #16. Diet samples drawn from the top, middle, and bottom of the mixing vessel in weeks 1, 2, 3, 4, 13 and at 13 weeks intervals thereafter were analyzed for homogeneity and drug levels. The drug concentrations in the diets were adjusted weekly for the first 14 weeks of treatment and biweekly thereafter.

2. **Test Animals**

Five to six weeks old male and female CD rats weighing 124 to

281g were used in this study.

B. **Study Design**

1. Animal Assignment

For oncogenicity phase of the study, animals were assigned randomly into control, 0.15, 0.5 and 1.5 ppm/day groups. Each group contained 60 rats/sex. In addition, 10 rats/sex/group were maintained in the satellite phase of the study.

2. Duration of Treatment

Rats in the oncogenicity phase were fed at least for 104 weeks. Control rats from the satellite group were also maintained for 104 weeks.

C. **Observations/Determinations**

Except for a few minor changes, rest of the examinations and determinations were similar to study #16. Fasting blood samples for hematology and serum chemistry were collected after 101 weeks of treatment. For drug absorption part of the study, blood samples were drawn from all survivors after 103 weeks of treatment. No urine samples were collected.

Reported Results

1. **Clinical Observations and Mortality**

No unusual signs of toxicity were observed. The mortality in week 104 ranged from 73% (MD females) to 85% (MD males).

2. **Food Consumption and Body Weights**

No intergroup differences were observed. Food conversion efficiency was similar in all groups, and dietary analyses indicated that drug levels were close to the nominal values.

3. **Ophthalmoscopy**

No drug-related changes were observed.

4. **Hematology and Blood Chemistry** In males receiving 0.5 mg/Kg/day CD 271, the values of packed cell volume (-12%), Hb concentration (-12%) an RBC counts (-11%) were significantly ($p<0.05$) lower than the controls. In addition, a few randomly distributed but statistically significant changes were not considered drug related.

   The activities of plasma alanine and aspartate aminotransferase were decreased (15-57%, $P< 0.05$) in all drug treated male groups; in females alanine aminotransferase (29-52%, $p< 0.001$) activity was declined. Plasma glucose concentration was significantly increased (16-21%; $p<0.05$) in drug treated males, no changes were observed in females. Plasma triglcyride concentrations were significantly high (67-68%, $p< 0.01$) in mid-and high-dose males. No dose related trend was observed in any of the changes in hematological or blood chemistry parameters.

5. **Plasma Drug Level**

   The mean group plasma drug concentrations (males 1-9, 18,22 and females 10,19,26 ng/mL) after 103 weeks of treatment were dose related.

6. **Macroscopic Pathology and Organ Weights**

   Enlarged adrenal glands were observed in all the drug treated groups of both sexes. Absolute adrenal weights in males (36,23 and 36) and females (197 113 and 14%) were significantly increased. The corresponding relative weights were 19, 21,31% and 240, 105, and 8%, respectively. The absolute (-44%) and relative (-35%) weights for ovaries were decreased in the low dose females, however, weights were increased in mid (132 and 144%) and high dose females (126, and 108%).

7. **Histopathology** A number of drug related histopathological changes were observed in rats found dead during the

Table 1. Summary of Neoplastic Lesions in Rats Found Dead, Killed *In extremis*, or Sacrificed After 104 Weeks of Treatment.

ORGANS/LESIONS	MALES CONT.	MALES LD	MALES MD	MALES HD	FEMALES CONT.	FEMALES LD	FEMALES MD	FEMALES HD
Adrenal medulla L + R	60	60	60	60	60	60	60	60
Malignant pheochromocytoma	2	3	0	3	1	1	2	3
Benign pheochromocytoma	7	9	10	18	6	3	6	3
Liver	60	60	60	60	60	60	60	60
Hepatocellular carcinoma	1	3	1	3	0	1	0	1
Pancreas	60	59	60	59	59	60	60	60
Islet cell carcinoma	1	4	4	4	0	1	1	0
Islet cell adenoma	2	4	2	5	1	1	1	2
Exocrine cell adenoma	0	0	1	0	0	0	0	0
Pituitary	60	60	60	60	59	59	60	60
Carcinoma	0	0	1	1	0	1	0	0
Granular cell tumor	0	1	0	0	0	0	0	0
Adenoma	30	25	24	25	46	45	45	45
Thyroids (L + R)	56	58	59	57	60	59	60	60
Follicular cell carcinoma	0	2	2	0	0	0	1	1
Follicular cell adenoma	2	1	0	1	0	1	0	4
Parafollicular Cell carcinoma	1	2	2	3	1	0	3	0
Parafollicular cell adenoma	5	1	5	0	2	4	5	4
H' poetic tumor	60	60	60	60	60	60	60	60
Monocytic leukemia	1	2	2	4	0	2	1	0
Malignant lymphoma	1	1	2	0	0	0	1	0
Histiocytic sarcoma	0	0	0	2	0	0	2	0
Skin	31	36	20	35	51	55	51	51
Sarcoma	4	4	3	3	1	1	2	0
Papilloma	3	3	2	3	1	0	1	0
Keratoacanthoma	2	4	3	6	0	0	0	0
Lipoma	3	7	2	4	0	0	0	0
Fibroma	4	5	0	4	1	1	4	3

a. Number of organs examined are underlined.

study, sacrificed in extremis, or after 104 weeks of treatment (tables 1 and 2). The high-dose males exhibited a significant ($p < 0.05$) incidence of benign pheochromocytoma of the adrenals. The combined numbers of benign and malignant pheochromocytomas and pancreatic islet cell tumors in drug-treated males indicated a higher incidence. A high incidence of carcinomas and adenomas of thyroids was observed in drug treated females (Table 1).

Significant drug related non-neoplastic changes included adrenal medullary hyperplasia in both sexes, and centriacinar hepatocytic fatty vacuolation and extramedullary

Table 2 Summary of Non-neoplastic Lesions in Rats Found Dead, Killed in extremis or Sacrificed after 104 Weeks of Treatment.

ORGAN/LIAISONS	MALES				FEMALES			
	Cont.	LD	MD	HD	Cont.	LD	MD	HD
Adrenal cortex (L+R)	60	60	60	60	60	60	60	60
Cortical fatty vacuolation	17	11	10	10	2	2	6	3
Cortical hemorrhagic degeneration	5	6	7	5	37	46	42	41
Focal cortical hypertrophy	2	3	3	0	1	0	0	0
Focal cortical hyperplasia	2	2	2	2	0	2	1	2
Adrenal medulla (L+R)	60	60	60	60	60	40	60	60
Focal medullary hyperplasia	7	12	9	13	4	3	5	11
Brain	60	60	60	60	60	59	60	60
Depression due to enlarged pituitary	6	8	12	7	12	22	15	17
Hemorrhage	1	0	3	1	1	0	3	0
Liver	60	60	60	60	60	60	60	60
Centriacinar hepatocytic fatty vacuolation	7	8	11	8	30	34	37	44
Periacinal hepatocytic fatty vacuolation	1	8	4	12	1	3	2	4
Foci of leucocytes within sinusoids	3	5	3	4	5	4	10	7
Extramedullary Hemopoesis	1	0	1	0	3	6	5	10

Stomach	60	60	59	60	60	60	60	60
Glandular region								
Fibrosis of lamina propria	3	2	7	7	2	2	3	1
Keratinized region Ulcer (s)	0	3	6	1	4	1	0	1
Hyperkeratosis and acanthosis	4	7	7	5	4	2	2	4
Chronic inflammation	0	3	6	3	3	1	1	1
Testes (L + R)	60	60	60	60	0	0	0	0
Degeneration of tubular germinal epithelium	10	14	16	9	0	0	0	0
Tubular mineralization	0	3	1	2	0	0	0	0
Arteritis with hyaline degeneration	12	18	17	7	0	0	0	0
Thyroids (L + R)	56	58	59	57	60	59	60	60
Focal parafollicular cell hyperplasia	4	5	5	4	10	10	6	14
Multicentric parafollicular cell hyperplasia	6	3	8	5	13	17	10	14
Urinary bladder	60	60	60	59	60	60	60	60
Transitional cell hyperplasia	0	3	3	1	0	0	0	0
Uterus	0	0	0	0	60	60	60	60
Focal hyperplasia of endometrial stroma	0	0	0	0	1	4	4	1
Vascular mineralization	0	0	0	0	2	3	3	10

Number of organs examined are underlined.

hemopoiesis in females. When compared to controls, a high incidence of periacinar hepatocytic fatty vacuolation was observed in male rats. High incidence of chronic inflammation (stomach), tubular mineralization (testes), and transitional cell hyperplasia (urinary bladder) were observed in males. High dose females indicated a higher incidence of uterine dilation.

18. CD 271® Aqueous Gel Suspension: Oncogenicity Study by Topical Application to CD-1 Mice for their Life Span (MD/92071; 1989-1991).

Facilities:

A. MATERIALS AND METHODS

1. Animals: Five to six weeks old CD-1 male and female (10-

34g) mice.

2. **Test substance** Lot numbers and concentrations tested:

1. 0.0% CD 271 524. 635/2P/F2
2. 0.03% CD 271 524.687/F1
3. 0.1%CD 271 524. 635/2/F3
4. 0.3% CD 271 524. 697/1/F2

B. **STUDY DESIGN**

1. **Animal Assignment and Drug treatment**

Fifty mice of each sex per dose group received topical applications of CD 271 aqueous gel suspension on the clipped dorsum at concentrations of 0.03, 0.1 or 0.3% (W/W) at a dose volume of 2 mL/Kg corresponding to dosages of 0.6, 2.0, or 6.0 mg/Kg/application. First control group received the vehicle gel alone at the same frequency as the drug treated group. The second (negative) control group was simply clipped and received no gel applications.

2. **Duration of Treatment**

For the first 19 weeks of the study, test substance/vehicle were applied seven times a week. However, because of severity of dermal lesions at the application sites, the frequency of gel application was reduced to 5 times/week. For the same reason, frequency of application was further reduced to 3 times/week from week 63 onwards. High dose males and females received treatment for 98 and 101 weeks, respectively. Other groups were treated for 104 weeks.

Additional satellite groups containing 20 mice/sex/group were treated for 52 weeks and then sacrificed. These animals were used solely for blood chemistry and to investigate absorption.

C. **OBSERVATIONS/DETERMINATIONS**

1. **Dermal Reactions and Clinical Signs**

Mice were examined daily for signs of toxicity, morbidity, and mortality. More detailed examinations including palpation were conducted weekly. Application sites were examined for dermal lesions (irritancy) 24 hours after the first application each week. Erythema was graded on a 5-point scale from absent to severe. Exfoliation, fissuring and scabbing were recorded as present/absent. Animal was recorded as being overactive if it was hard to remove the mouse from the cage. Mice judged to be *in extremis* were killed.

2. **Body Weights and Food Consumption**
Body weights were determined weekly during the first 14 weeks of treatment and biweekly thereafter. Food consumption was recorded weekly throughout the treatment period.

3. **Hematology And Blood Chemistry**
Blood Samples drawn from 10 mice/sex/group during week 95 were used to determine packed cell volume (PCV), Hb concentration, erythrocyte, total and differential leucocyte and platelet counts. Samples for determination of plasma alkaline phosphatase were collected from 4 mice/sex of the satellite groups after 4, 11, 24, 37 and 50 weeks, and from 5 mice/sex of oncogenicity groups 2-5 in week 91 of treatment.

4 **Plasma Drug Levels**

Blood Samples for determination of plasma drug levels were collected from 4 mice/sex of the satellite groups in weeks 6,13,26,39 and 52, and from 5 mice/sex of groups 2-5 of oncogenicity phase.

5. **Gross Pathology and Organ Weights**

All mice in oncogenicity phase were subjected to detailed necropsy examination, and 8 major organs were removed and weighed.

6. **Histopathology**

Nineteen organs/tissues obtained from all mice of groups 2 and 5 and all mice found dead or sacrificed moribund in groups 3 and 4 were subjected to histopathologic examination.

REPORTED RESULTS

1. **Dermal Reactions**
Drug and dose-related signs of skin irritancy were observed in all mice administered CD 271 aqueous gel. The intensity of lesions particularly in the early and later parts of the study, was more severe in females. Erythema was first observed in week 3 in 63% of drug treated mice. The number of mice with erythema increased with an increase in the treatment period, and by week 18 all drug treated mice were affected. Minimal signs of irritancy were occasionally observed in controls.

After reduced frequency of application in week 20, the severity of erythema in all drug treated mice declined until week 49 for males and week 37 for females. Subsequently, the severity of lesions began to increase in all groups. An incidence of moderate to severe erythema was observed in high dose mice during weeks 58 to 62.

Following a further reduction in frequency of applications during week 63, the severity of lesions again declined in all drug treated mice. In the low dose males, the number of mice affected with erythema was also reduced. Lesions were graded from very slight to well-defined.

A majority of animals receiving CD 271 exhibited exfoliation throughout the treatment period. Fissuring was seen occasionally. Scabbing was observed in mid-and high-dose mice from week 12 onwards. Similarly, skin thickening was observed throughout the study period in drug treated mice.

Overactivity broadly correlated with irritancy was rarely observed after the second reduction in frequency of application.

Skin abrasions including ulcerative lesions around the margins of application sites were first observed in week 11 in CD 271 mice. However, despite the reductions in frequency of application, abrasions continued to develop. The incidence of abrasions was also dose dependent.

2. **Palpable Swellings**

The palpable swellings exhibited a dose-dependent increase in number with a decrease mean onset time of appearance. The multiplicity (i.e, number of mice bearing the swellings) of such masses was significantly ($p<0.05$ to $p<0.01$) high in mid- and high-dose animals. These subcutaneous swellings were frequently found in the groin region, particularly during the first-half of the study. In many cases a partial regression was observed, a proportion appeared as enlarged lymph nodes at necropsy and malignant lymphomas, sinus histiocytosis or parafollicular hyperplasia at histopathological examination.

3. **Mortality**

Because of severity of abrasions and ulcerations particularly in high-dose males, a good number of affected mice were sacrificed on humane grounds (Table 1)

TABLE 1. Group Distribution Of Mice Sacrificed On Humane Grounds

Group	CONT 1	CONT 2	LD	MD	HD	CONT. 1	CONT 2	LD	MD	HD
No Animals	2	1	5	5	20	2	0	1	6	6

The survival rates at the end of the study period were as follows:

GROUP	PERCENT SURVIVAL	
	MALES	FEMALES
Control. 1	44	48
Control. 2	48	54
LD	44	42
MD	30	38
HD	32	30

4. **Body Weights and Food Consumption**

No statistically significant intergroup differences were observed. The efficiency of food utilization (i.e, food convresion ratios) in drug treated mice was similar to vehicle control during the first 14 weeks of the study.

5. **Hematology and Blood Chemistry**

Hematological parameters exhibiting significant ($p < 0.05$ to 0.01) differences included decreased (14-18%) platelet counts in mid-and high-dose males and increased (41.%) lymphocytes in high dose males. No intergroup differences in blood chemistry were observed.

6. **Plasma Drug Levels**

At week 38, the mean plasma drug concentrations in low-and mid-dose males were 36.0 and 117.8 µg/mL, respectively. No samples in high-dose males were available for analysis. No detectable plasma levels were found in low-dose females. (detection limit 2µg/mL). Samples from mid-and high dose mice contained 86.2 and 180.4 µg/mL CD 271, respectively. Reportedly, mean plasma levels exhibited no clear trend with time during the study despite having altered the frequency of dosing.

7. **Gross Pathology and Organ Weights**

Drug related macroscopic lesions were mainly restricted to the skin (Table 1) The intensity of lesions was more severe in the high dose group of both sexes.

TABLE 1 SUMMARY OF DERMAL LESIONS IN MICE FOUND DEAD, KILLED MORIBUND AND SACRIFICED AT STUDY TERMINATION

LESION GROUPS*	1	2	3	4	5	1	2	3	4	5
Treated Skin	50	50	50	50	50	50	50	50	50	50
Encrustation (s)	1	0	4	6	11***	1	0	3	4	6*
Excoriation (s)	0	0	1	3	7*	0	0	0	3	4
UNTREATED SKIN										
Encrustation (s)	2	4	9	4	16**	1	1	2	8	5
Excoriation (s)	2	1	3	3	9*	2	1	0	1	1
Hairless moderate	9	4	8	4	15**	11	8	16	15	8*
Masses Present	3	4	4	8	12	14*	5	8	14*	9
Masses Not apparent	11	6	10	18**	21**	6	7	7	8	15

*Group, 1 Control, 2, vehicle control, 3. Low dose, 4. Mid-dose, 5 High dose *P< 0.05 **P< 0.001 ***P< 0.001

8. Histopathology

In histopathological examinations of two male control groups, only vehicle control group was examined. Also in females, only a limited number of tissue/organs in the negative control group were subjected to histopathological examination. This made it impossible to elucidate the tumor promotional effect (if any) of vehicle. In fact, in many instances, the lesions in the vehicle control groups were similar to or higher than the drug treated groups. Although no dose related trend was observed, the number of males bearing tumors was much higher in the drug treated groups (Table 2). Thus, when compared with the vehicle control group, the incidence of neoplasms was 250, 125, and 50% higher in the low-, mid-and high-dose males. The incidence was much lower in females. Whereas the incidence of pulmonary tumors was similar in the male groups, in females incidence was much high (53%) in the vehicle control group.

Once again, non-neoplastic dermal lesions were more prevalent in males, and the incidence in the vehicle control group was minimal, indicating that lesions were drug related (Table 3). The number and intensity of majority of lesions was dose related. The incidence of acanthosis in drug treated mice was almost hundred percent. This incidence was also very high (22-24%) in the untreated skin indicating application of drug through paws etc. The lesions of adrenal cortex (focal, hyperplasia and hypertrophy) were much more prevalent in the males. Chronic inflammation of the liver was very high (34-44%) in control and drug treated groups, and was only 6% in the negative control group in females.

TABLE 2 Summary of Neoplastic Lesions in Mice found dead, Killed *in extremis*, and Sacrificed at Study Termination.

	MALES					FEMALES				
ORGAN/LESIONS	1[a]	2	3	4	5	1	2	3	4	5
Adrenal Cortex (L+R)	0	50	49	50	47	0[b]	50	49	50	50
Benign cortical adenoma	0	1	3	2	2	0	1	0	0	0
Adrenal Medulla (L+R) Benign pheochromocytoma	0	0	0	0	0	0[b]	0	1	1	0
Liver	0	50	50	50	50	50	50	50	50	50
Hepatocellular carcinoma	0	2	9*	5	3	0	0	1	0	0
Hemangiosarcoma	0	2	3	2	2	1	1	2	1	1
Hepatocellular adenoma	0	0	0	2	1	0	0	2	0	0
Hemangioma	0	0	2	1	0	1	0	0	1	0
Lungs	0	50	32	39	50	17	50	34	35	50
Pulmonary carcinoma	0	8	5	7	4	4	5	2	3	0
Pulmonary adenoma	0	3	3	6	2	5	7	4	0	2
Hemopoietic Tumors	[b]	50	50	50	50	50	50	50	50	50
Hemangiosarcoma	0	7	8	10	5	9	5	11	9	10
Spleen	0	49	50	50	50	50	50	50	50	50
Hemangiosarcoma	0	0	1	1	1	0	0	1	1	2
Hemangioma	0	0	0	1	1	1	0	0	0	1

a. Number of organs examined are underlined.

b. No tissues were examined

*$p < 0.05$

Table 3. Summary of Non-neoplastic Lesions in Mice Found Dead, Sacrificed Moribund and Killed at Study Termination.

Organ/Lesion/Group	1	2	3	4	5	1	2	3	4	5
Adrenal Cortex (L + R)	0	50	49	50	47	0	50	49	50	50
Focal cortical hyperplasia	0	10	11	7	6	0	0	0	0	1
Focal cortical hypertrophy	0	1	5	9*	3	0	0	0	0	1
Cecum	0	50	28	35	50	0	49	29	31	50
Lymphoid hyperplasia	0	7	0	2	0	0	5	2	0	10
Duodenum	0	50	25	35	49	0	50	29	31	50
Sphincter of ODDI present	0	5	1	4	5	0	7	4	1	6
Eye, Left Lenticular degeneration	0	50	31	36	50	18	50	31	33	50
	0	0	0	0	0	4	4	2	1	1
Kidneys	0	50	50	50	50	5	50	50	50	50
Progressive (senile) nephropathy	0	7	11	10	6	2	10	12	8	12
Cortical lymphocytic infiltration	0	4	6	3	3	0	5	7	9	5
Cortical cyst (s)	0	15	8	7	5*	0	1	1	1	1
Basophilic cortical tubules	0	5	4	3	8	0	1	2	1	3
Lymphnode Mesenteric	0	50	31	41	49	15	46	37	37	45
Erythrocytes and erythrophagocytosis in sinuses	0	12	10	11	8	9	15	9	8	7
Liver	0	50	50	50	50	50	50	50	50	50
Nodular hyperplasia	0	7	7	10	6	0	0	0	0	1
Chronic inflammation	0	22	14	17	16	3	20	20	21	17

Skin Treated x4	0	50	50	50	50	2	50	50	50	50
Acanthosis	0	4	50	49***	48***	0	3	50***	50**	50***
Hyperkeratosis	0	1	26***	38***	44***	0	0	31***	44***	47***
Scab (s)	0	3	23**	32**	38***	0	0	24***	23***	36***
Ulcer (s)	0	1	7	14***	24**	0	1	1	6	10**
Diffuse subcutaneous inflammation/ collagen deposition	0	0	27**	37***	43***	0	0	38***	43***	42***
Increased superficial follicles	0	1	1	1	8**	0	0	0	3	7*
Atrophy of glandular and or follicular structures	0	1	12**	9***	26***	0	0	3	9**	12***
Skin Untreated	0	50	50	49	50	2	50	50	49	50
Acanthosis	0	1	2	1	12**	0	2	1	4	11*
Spleen	0	49	50	49	50	50	50	50	50	50
Extramedullary hemopoiesis	0	8	11	14	26***	14	18	22	22	21

*p<0.05, **p<0.01, ***p<0.001

LABELING

Carcinogenesis, Mutagenesis, Impairment of Fertility

The draft for labeling must be corrected to include the actual doses administered, not the nominal values described in the protocol. In addition, the text should reflect the actual preclinical findings. Because of severe drug and dose-related dermal reactions, the topical oncogenicity study in mice was compromised. The frequency of application was reduced from seven (18% of the study time) to five (42%) to three (40%) times per week. Thus, the doses administered during the last part of the study were approximately 1/3 of the nominal values.

The modified draft should read as follows: Lifetime studies with adapalene have been completed in mice at topical doses of 0.4, 3 and 10 mg/m^2/day (a topical dose in humans is 3.0 mg/m^2/day) and in rats at oral doses of 0.9, 3 and 9 mg/m^2/day. Oncogenicity studies revealed that drug was tumorigenic in both species. No photocarcinogenicity studies were conducted. However, animal studies have an increased tumorigenic risk with the use of related drugs (e.g., tretinoin) when exposed to UV light in the laboratory or in the sunlight. In a series of in vivo and in vitro studies, adapalene did not exhibit mutagenic or genotoxic activities.

Pregnancy:

Teratogenic Effects. Pregnancy Category C. Adapalene administered orally up to 100 and 240 times (mg/m^2/day) of the human dose has been shown to be teratogenic in rats and rabbits. Dermal teratology studies conducted in rats and rabbits at 4-8 times (mg/m^2/day) the human dose exhibited no phototoxicity in rabbits, and only minimal increase 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.

TOXICOLOGIST'S DISCUSSION AND INTERPRETATION OF SAFETY DATA

Biodisposition and long-term studies clearly indicated that adrenal glands were the primary target of adapalene toxicity in both sexes of animals. In an intravenous tissue distribution rat study, except for ovaries, the highest amount of radioactivity was found in the adrenals. Though the amount of radioactivity found in the tissues and carcass accounted for only 3.4% of the administered dose, the tissue radioactivity decreased at a very slow rate, and 56 days after dosing, adrenals and ovaries still retained significant amounts of radioactivity. In rabbit subchronic and chronic dermal studies, essentially non-linear plasma drug levels remained fairly stable throughout the treatment period, and elimination into bile was limited and slow.

Irrespective of the fact that adrenals were the primary target for binding (biodisposition studies) and tumorigenesis no attempt was made to asses the function of the glands by determining the blood cortisol and levels of cortisol and its metabolites in the urine.

Two oral (rats) and one dermal (mice) oncogenicity studies were conducted. In the first oral study, 15 and 25% incidence of malignant and benign pheochromocytoma of adrenal medulla were observed in the high dose males. The combined incidence for pheochromocytoma (benign + malignant) in the same group was 30% of the control.

In the second oral oncogenity study, the combined incidence of pheochromocytoma in male groups was as follows:
control, 15%
low-dose, 29%
mid-dose, 17%
high-dose, 35%

In addition, the incidence of islet cell carcinoma of pancreas was 2% in the control group and 7% in each of the drug treated male groups. The combined incidence of pancreatic tumors (islet cell adenoma and carcinoma) was 5% in control, 16% in low-dose, 10% in mid-dose and 15% in high-dose groups, respectively.

The dermal oncogenicity study was badly compromised. In this study, mice at all dose levels were extremely intolerant of adapalene. In a futile attempt to rescue the study, the frequency of drug application was arbitrarily reduced from 7 to 5 to 3 times per week. The nominal dose levels mentioned in the protocol were applied only for the first 19 weeks or for 18% of the total treatment period. Thereafter, the reduced levels were administered for 42 and 40% of the treatment period, respectively. During the last phase (40% of the treatment period), mice received only about 1/3 of the nominal dose levels. Irrespective of such drastic changes in the protocol, the intensity and severity of dermal abrasions and ulcerations particularly in the high dose males led to an *in extremis* sacrifice of a substantial number of mice.

Drug and dose dependent dermal lesions (acanthosis, hyperkeratosis, scabs, ulcer) involved 50 to 90% mice of both sexes.
Histopathologic examinations for neoplastic and non-neoplastic lesions in males did not include any tissues/organs from the

the female negative control group. Such data make it impossible to assess the promotional effect(s) of vehicle on tumorigenesis. It must be mentioned that in many cases frequency of dermal lesions in the vehicle group was similar to drug treated groups.

In rat oncogenicity studies, neoplastic and nonneoplastic lesions were observed at the lowest dose tested, hardly leaving any margin of safety. In the dermal study, a statistically significant ($p<0.0174$) incidence of hepatocellular carcinoma was observed in low-dose males. At this dose level, margin of safety is 0.15 times of the clinical dose.
Also in the female spleen, a significant <u>positive</u> linear trend in combined incidence of hemangiosarcoma and hemangioma was observed. There is no other long term dermal study available to judge if only mouse skin is hypersensitive to adapalene, and therefore much more drug was transfered to the systemic circulation. In the current study it seems each drug level acted as a non-toleratled dose.
In absence of any data on chronic use in humans, these observations are alarming.

Tumor data of all oncogenicity studies require an extensive statistical analysis to reach to a definite conclusion. However, the study authors have frankly admitted that adapalene was carcinogenic/tumorigenic in both oral studies. This reviewer strongly feels that drug was also tumorigenic in the dermal study. Based on the tumor data of two oral studies, the study authors have reached to the following conclusions.

1. "These neoplastic changes are considered to have no relevance to the topical use of CD 271 in humans in clinical conditions". and

2. "In conclusion, the observation of an increased incidence of pheochromocytomas, initially observed in male rats after and interim 78 week sacrifice and subsequently confirmed after the terminal 104-week sacrifice is not an unexpected finding. Both isotretinoin and retinol acetate have shown similar changes. Pheochromocytoma is an idiosyncratic occurrence in male rats that has been observed in chronic toxicity studies with a number a different types of drugs. It was not seen in the mouse oncogenicity study, and it is not relevant to man where the occurrence is rare."

In reaching to such conclusions, the study authors have completely ignored the incidence of tumors other than pheochromocytomas. Reportedly, adapalene was nonmutagenic and nongenotoxic in animal studies. But it probably was oncogenic in two rodent species. Why then epigenetic mechanism (peroxisome proliferation) was not evaluated? It must be mentioned that a significant incidence of hepatocellular carcinoma was observed in the topical oncogenicity study.

RECOMMENDATIONS

1) Tumor data were evaluated by Dr. Daphne Lin, Mathematical Statistician. A summary of her findings is quoted below. Her review is enclosed.

"In the 78-week rat chronic toxicity phase, results of tumor data analyses showed that there was a significant positive linear trend in adrenal benign and malignant pheochromocytomas (p = 0.0003) in male rats. Noted that there are only 20 animals per sex/group in this study. The results of tumor data analyses of 104-week rat oncogenicity study showed that there were significant positive linear trends in thyroids follicular cell adenoma and carcinoma combined (p = 0.0049) in female rats and in adrenal benign and malignant pheochromocytomas (p = 0.0051) in male rats. There were marginally significant positive linear trends in H'poietic histiocytic sarcoma (p = 0.0696) and in H'poietic monocytic leukaemia (p = 0.0696) in male rats. Similar results were found when the tumor data of both rat studies were combined.

In the mouse study, results of the tumor data analyses showed that there was a significant positive linear trend in the spleen hemangiosarcoma and hemangioma (p = 0.0372) in female mice when vehicle control, low, medium, and high dose groups were considered."

As it stands, from preclinical view point this drug can not be approved. However, if Review Dermatologist feels comfortable with the available clinical data and his own experience then the approval of this drug for human use should rest with him.

2.) In case this drug is approved, the sponsor should be advised to correct the preclinical portion of the labeling. It must include actual data and facts mentioned under labeling in this review.

Kumar Mainigi 6/6/94

Kumar D. Mainigi, Ph.D. DABT
Toxicologist

CC: Orig. NDA 20-338
HFD-340
HFD-520
HFD-502
HFD-540/Sup.Pharm/~~Rotberberg~~ ALAM FWA 6/13/94
HFD-540/Pharm/Mainigi
HFD-520/Chem/Timper
HFD-540/MO/Franz
HFD-540/CSO/Cook
HFD-520/Micro/Dionne
smh-6/3/94
HFD-520/mo/Bostwick
WAC 7/10/94

Results of non-clinical trials will be incorporated into the labeling when the application becomes approvable from a clinical prospective

Date: 6-24-94

To: DR Taylor, A.
Chairman, CAC Executive Committee
FROM: KUMAR D. MAINIGI, PH.D., DABT
Toxicologist, HFD-540
SUBJECT: Comments on CAC Draft, NDA 20-338 (Adgalene

Dose-Range Finding Studies

In the second dose-range study (p.17 main review), only oral doses of 0.15 and 0.5 were tested. Therefore, hematological and biochemical changes were observed at these levels, not at 1.5 mg/kg/day level.
In addition to anemia, progressive remodeling of bone marrow can also lead to leukemic changes.

MOUSE DERMAL STUDY

No dose-range finding study was conducted, therefore, dose and species selections were arbitrary. Progressive derma lesions due to total intolerance to drug exist in 3 weeks of treatment. Apparently, mouse was not a suitable species to test this drug. A fact that must have had revealed itself in a dose-range finding study. Historically dermal carcinogenicity and promotion studies were conducted in mice. However, over the years it has been realized that the reactivity of the skin of the albino rat is much more similar to the reactivity of human skin. In fact, in recent years albino rat has been increasingly utilized in the repeated cutaneous toxicity studies (Hermansky S.J., cutaneous Toxicology p-771; In: General and Applied Toxicology Vol 1, Eds. Ballantyne, Marrs and Turner, Stockton Press, 1993).

One fact must be mentioned that pig skin is morphologically more similar to human skin, however, for various reasons pigs cannot be used in long term studies.

The doses mentioned in the CAC report (0.6; 2.0; and 6.0 mg) are the proposed nominal doses, not the actual doses received by the animals. The frequency of drug application was decreased twice from 7 to 5 to 3 times per week. The nominal doses were applied only for about 18% of the total study period. My calculations indicate that on the average

HD group received 3.3 mg/Kg/day (~ 9.9 mg/m²/day)
MD " " 1.14 " " " (~ 3.4 mg/m²/day)
LD " " 0.44 " " " (~ 1.3 mg/m²/day)

Reportedly, based on dermal lesions, all doses exceeded MTD.

Proposed clinical dose is ~ 3 mg/m²/day. It simply means that the lowest MTD (~ 1.3 mg/m²/day) was much lower than the clinical dose! Customarily, margin of safety is calculated using NOEL, not MTD.

The integrity and mosaic of skin structure was completely destroyed. Dermis has hydrocarbon activating enzymes. These entities probably never had a chance to express their catalytic activities.

It also must be mentioned that this drug was exempted from photocarcinogenicity testing. Though in my opinion this molecule is a suitable candidate for photocarcinogenicity testing.

FIRST ORAL STUDY IN RATS

Because of a small number of animals (20/sex/dose) and short-period of treatment, this study should not be classified as carcinogenicity study.

SECOND ORAL STUDY IN RATS

The study director though overemphasized the mechanistic relevance of pheochromocytomas, completely ignored the presence of other tumors. No historical data for these tumors were provided for a comparison. The fact remains that multiple tumors were observed in this study, and this was the only study conducted properly. I am not qualified as a biostatistician to start a debate on the significance of "positive linear trend." but still I strongly feel that this positive indicator revealed in a small number of animals at doses not very different from the clinical doses, might turn into a reality in large populations of acne patients.

cc:

Bio

OCT 1 1993

NDA 20-338 **SUBMISSION DATE:** March 19, 1993

DIFFERIN™
Adapalene Topical Solution
OWEN/Galderma Laboratories, Inc.
Post Office Box 6600
Fort Worth, Texas 76115

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: New Molecular Entity **Code 1S**

I. SYNOPSIS:

The sponsor has submitted NDA 20-338 which was filed on March 19, 1993 for Differin™ (Adapalene Topical Solution). The proposed drug product contains adapalene 0.1% w/v (1 mg/ml) in an alcoholic solution and is indicated for topical application in the treatment of acne vulgaris. Differin™ solution should be applied to the affected areas of the face, chest, and back once a day before retiring and after washing. A thin film of the solution should be applied, avoiding eyes, lips, and mucous membranes.

Nine studies were conducted to evaluate the *in vitro*, biopharmaceutic, and pharmacokinetic characteristics of adapalene. These studies include; three *in vitro* (PK 91007, PK 91005, and TILL/90402), two biopharmaceutic (CIR 89001 and PC 86020), and four clinical trials (PC 86012, PC 86013, PC 86030, and CR 88043). Specifically, studies PK 91007, PK 91005, and TILL/90402 were conducted to assess the interspecies hepatic metabolism, liberation-cutaneous penetration, and blood/plasma protein binding. Studies CIR 89001 and PC 86020 were performed to investigate the pharmacokinetics, metabolic profile, and liberation of adapalene after single topical application of this drug. Studies PC 86012, PC 86013, PC 86030, and CR 88043 represent four controlled clinical studies where the plasma levels of adapalene were monitored during the clinical trials to assess the systemic absorption of this drug after multiple topical applications.

The results from the biopharmaceutic and clinical studies indicate that no quantifiable levels of parent drug were found in the plasma of human patients following single or chronic application of 0.1% adapalene solution (detection limit of 1 ng/ml). However, after cutaneous application of 0.1% ^{14}C-adapalene solution some traces of radioactivity (0.02-0.06%) were found in the faeces of the human patients, showing that a fraction of adapalene can be absorbed after topical administration to the skin.

Overall, the results from these studies indicate that the systemic absorption of adapalene after topical administration is very low.

II. RECOMMENDATION:

The Division of Biopharmaceutics has reviewed NDA 20-338 which was filed on March 19, 1993 for Differin™ Solution. Based on the information submitted under *in vitro* (PK 91007, PK 91005, and TILL/90402), biopharmaceutic (PC 86020 and CIR 89001), and clinical studies (PC 86012, PC 86013, PC 86030, and CR 88043), the Division of Biopharmaceutics considers that the sponsor has provided sufficient *in vitro/in vivo* data to support the product's approval, and this submission is acceptable.

Regarding the proposed package insert, it is also acceptable, provided the addition of new information and the changes that are proposed are incorporated into the Pharmacokinetics part of the Clinical Pharmacology section of the labeling. The sponsor should re-submit the package insert for review when all changes have been incorporated.

Please convey the Recommendation as appropriate, and Package Insert Comments (pages 13 and 14) to the sponsor.

NOTE: Attachments I to VI are being retained in the Division of Biopharmaceutics and may be obtained under request.

TABLE OF CONTENTS Page No.

III. ORGANIZATION OF REVIEW

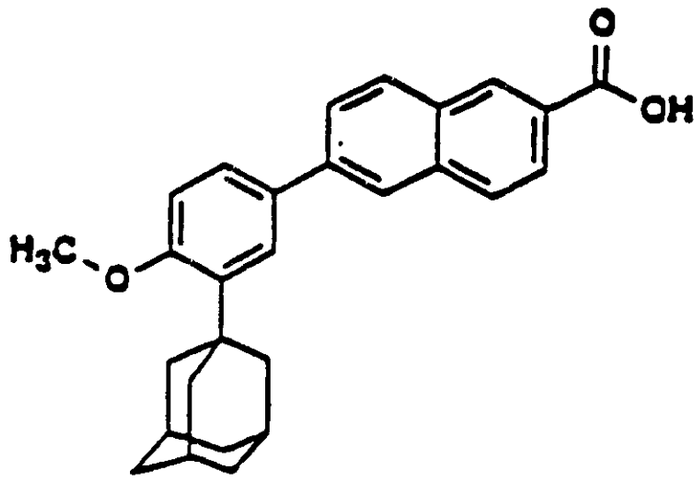
For reasons of clarity, this review will be organized as follows; First background information will be given, followed by drug formulation information. Then, an overall summary for the *in vitro*, pharmacokinetic, and clinical studies will be presented and the individual studies will be examined, and finally the package insert will be addressed.

IV. BACKGROUND

Adapalene is a chemically stable, retinoid-like compound. Adapalene is a potent modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Although the exact mode of action of adapalene is unknown, current evidence suggests that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Adapalene structural formula is as follows;

ADAPALENE



MF: $C_{28}H_{28}O_3$ MW: 412.52

V. DRUG FORMULATION

The proposed drug product contains adapalene 0.1% w/w (1mg/g) in an alcoholic solution dosage form for use topically in the treatment of acne vulgaris. The following is the quantitative composition of the proposed commercial formulation of adapalene solution:

Formulation I.D. No.: 50194

Ingredient	per gram	percent (w/w%)
Adapalene	1 mg	%
Polyethylene Glycol 400, NF	g	%
SD Alcohol 40-B, anhydrous*	gram	%

(Specific Gravity of finished dosage form =

*SD Alcohol 40-B, anhydrous, is a specially denatured alcohol supplied by the The formula for SD Alcohol 40-B, anhydrous, contains the following ingredients:

Alcohol - gallons
Tert-Butyl Alcohol - gallon

Table 1 presents a drug formulation development summary for biopharmaceutic studies PC 86020, CIR/89001, and PK 91005. Attachment I includes the quantitative compositions, lot numbers, and report locations for all the lots of the investigational formulations of adapalene solution that were used in pharmacokinetic studies, clinical pharmacology studies, and clinical trials.

TABLE 1

DRUG FORMULATION DEVELOPMENT SUMMARY TABLE

Study Number	Lot Number (Code Number)	Dosage Form and Strength	Batch Size
PC 86020 (DC/JF/91/141)	524416/F5 (S3)	0.1% adapalene solution	kg
	524635/2/F1 (G2)	0.1% adapalene aqueous gel	kg
	524645/F1 (G4)	0.1% adapalene alcoholic gel	kg
CIR/271/89001 (DC/JF/91-142)	^{14}C-271/008A/F1 (S3)	0.1% adapalene solution (radioactive)	g
PK 91005 (DCa/JF/92-020) (*in vitro*)	^{14}C-524416/R10	0.1% adapalene solution (radioactive)	g
	^{14}C-524635/R12	0.1% adapalene aqueous gel (radioactive)	g
	^{14}C-524827/R11	0.1% adapalene cream (radioactive)	g

VI. IN VIVO ANALYTICAL METHODS

A summary of the analytical methods used in the quantitation of adapalene in studies PC 86012, PC 86013, PC 86030, CR 88043, PC 86020, and CIR/89001 is presented in Table 3 (page 9). The validation information for the high performance liquid chromatography (HPLC) method(s) using fluorescence detection is presented in Attachment II.

VII. SUMMARY OF *IN VITRO*, BIOPHARMACEUTIC AND CLINICAL STUDIES

Table 2 list the *in vitro*, biopharmaceutic, and clinical studies included in the pharmacokinetic section of this NDA. These studies are summarized in Tables 4 to 6 (pages 10 to 12). Specifically, studies PK 91007, PK 91005, and TILL/90402 represent three *in vitro* studies conducted to assess the interspecies hepatic metabolism, liberation/cutaneous penetration, and blood/plasma protein binding. Studies CIR/89001 and PC 86020 represent two biopharmaceutic studies conducted to investigate the pharmacokinetics, metabolic profile, and liberation of adapalene after single topical application. Studies PC 86012, PC 86013, PC 86030, and CR 88043 represent four controlled clinical studies were the plasma levels of adapalene were monitored during the trials.

TABLE 2

Study Class	Place	Study Number	Type of Study
In Vitro	France	PK 91007	Interspecies hepatic metabolism
In Vitro	France	PK 91005	liberation/cutaneous penetration
In Vitro	France	TILL/90402	Blood and plasma protein binding
Biopharm	France	CIR/89001	PK & metabolism/single dose
Biopharm	France	PC 86020	Liberation/single dose
Clinical	Sweden	PC 86012	Tolerance/Efficacy (Adapalene sol 0.1% vs. vehicle)
Clinical	Sweden	PC 86013	Safety/Efficacy (Adapalene sol 0.1% vs. vehicle)
Clinical	Poland	PC 86030	Safety/Efficacy (Adapalene sol 0.1% vs. vehicle)
Clinical	Europe/multicenter (England, Germany, France, Italy, & Belgium)	CR 88043	Safety/Efficacy (Adapalene sol 0.1% vs. tretinoin gel 0.025%)

IN-VITRO STUDIES

***In Vitro* Hepatocyte Metabolism** *Study No. PK 91007 (CF/JF/92-080)*; *In vitro* metabolism studies were performed by incubating ^{3}H-adapalene with cultured hepatocytes of different species including man. The metabolism of adapalene by human hepatocytes was relatively rapid with almost no intact adapalene remaining in the medium after 24 hours under the chosen

conditions of culture. The major metabolite fractions found in the medium of the human hepatocyte culture corresponded to fractions M0/M1, M2, M6 and M7 of *in vivo* animal studies on the basis of retention times under specific chromatographic conditions. Although quantitative and qualitative differences in metabolite profiles were observed between the hepatocytes from the various species, metabolite profiles from human hepatocytes produced no previously unknown metabolite fractions and bore similarities to those of rat and dog (see Attachment III).

***In Vitro* Blood and Plasma Protein Binding** *Study No. TILL/90402 (DC/JF/91-143)*; In vitro studies revealed that more than 99% of adapalene was bound in human whole blood. About 26% was bound to erythrocytes with lipoprotein and human serum albumin accounting for the majority of plasma binding (see Attachment III).

Liberation/Penetration *Study No. PK 91005 (DCa/JF/92-020)*; A study was performed on human dermatomized skin, using a receptor fluid containing a surfactant and with an hourly flow rate/cell volume ratio equal to 1 during 15 hours. The two cm^2 skin surface was covered with 20 µl of formulation. Six different donors were used to compare the three formulations with twelve cells per formulation. After a 15 hr penetration, negligible radioactivity was detected in the receptor fluid. However, the quantity of radioactivity penetrated in the skin (dermis + epidermis) was significantly ($p>0.05$) higher with the gel formulation ($6.7 \pm 4.9\%$) than with the cream ($1.8 \pm 0.9\%$). See details of this study in Attachment III.

BIOPHARMACEUTIC STUDIES

Pharmacokinetic and Metabolic Profile of Adapalene after Single Topical Application *Study No. CIR/271/89001 (DC/JF/91-142)*; A study was performed in four male volunteers following a single topical non-occlusive but protected application of 0.5 ml of a solution containing 0.1% ^{14}C-adapalene to an area of 250 cm^2 on the upper back. Due to the extremely low quantities of radioactivity recovered, the original objectives of this study were restricted to simply measuring radioactivity in the biological sample collected. Pharmacokinetic parameters and metabolic profile data could not be generated.

An average 94% of the amount of the radioactivity applied was found in the excess removed from the surface 24 hours after application. Some traces of radioactivity were found in the faeces of each subject mainly between the third and the sixth day following the administration.

The amount measured accounted for about 0.02-0.06% of the administered dose. Some traces of radioactivity were also found in the plasma samples of two subjects but no significant radioactivity was found in the urine samples. The results show that under the conditions employed, absorption was 0.97-10.63% based on the proportion of the dose recovered from the skin surface or 0.02-0.06% based on faecal recovery. The discrepancy between these two methods of estimating the quantity absorbed might be attributable to an underestimation of the amounts non-absorbed due to technical problems of recovering all surface excess, although the possibility also exists of retention in the body during the period of observation and underestimation of the excretion (see Attachment IV).

Liberation of Adapalene in the Stratum Corneum In Vivo *Study No. PC 86020 (DC/JF/91-141)*; A study was performed in order to compare the liberation of adapalene following application of an aqueous gel, alcoholic gel, or alcoholic lotion formulations containing 0.1% adapalene to healthy human volunteers. The three formulations were applied at a dose of 50 µl to 7.5 cm^2 on the backs of twelve volunteers for periods of 1 and 24 hr. After removal of the excess, the drug was extracted from ten successive stripping of the stratum corneum and assayed by HPLC. After an application period of one hour, the quantity of adapalene found in the stripping was highest for the aqueous gel suspension and the alcoholic gel suspension (14% of the dose applied for both formulations). For the alcoholic lotion, the quantity found was approximately three times lower (4% of the dose applied).

After application periods of 24 hr, the quantities found in the strippings were lower for all three preparations, despite the presence of excess until just prior to the stripping procedure, namely 12%, 8%, and 0.4% of the dose applied for the aqueous gel, the alcoholic gel and the alcoholic lotion, respectively (see Attachment IV).

CLINICAL CONTROLLED STUDIES

Adapalene Detection in Plasma Samples During Clinical Trials *Studies PC 86012, PC 86013, PC 86030, and CR 88043*; Four controlled clinical trials were performed with adapalene solution 0.1% to evaluate in addition of safety and efficacy, the systemic absorption of adapalene after multiple topical application of Differin™ solution 0.1%. The results from these studies indicate that adapalene was not detected in the plasma samples of 29 acne patients treated with adapalene solution 0.1%. Limits of detection for adapalene of the HPLC assay methods were between ng/ml (see Attachment V).

TABLE 3

IN VIVO ANALYTICAL METHODS SUMMARY TABLE						
Study Number	Type of Biological Sample	Method Reference	Type of Method	Limit of Detection	Range ng/mL	Specificity (parent/metabolites)
PC 86012	Plasma	CIRD-M-007/271-7VE	HPLC Fluorescence detection	1 ng/mL		parent molecule
PC 86013	Plasma	CIRD-M-007/271-7VE	HPLC Fluoresence detection	1 ng/mL		parent molecule
PC 86030	Plasma	CIRD-M-007/271-7VE	HPLC Fluorescence detection	1 ng/mL		parent molecule
CR 88043	Plasma	CIR/271/89003	HPLC Fluoresence detection	0.15 ng/mL		parent molecule
PC 86020	Stratum corneum strips	CI 1187*	HPLC UV detection	50 ng/strip		parent molecule
CIR/271/89001	Plasma Feces Urine		Liquid scintillation counting	Plasma: 0.05 ng eq/g Feces: 1 ng eq/g Urine: 1 ng eq/g		total metabolic pool

* Methods report not available.

TABLE 4

IN VITRO STUDIES SUMMARY TABLE					
Study Number	**Type of Study**	**Test Article**	**Donor Species**	**Tissue Preparation**	**Parameters**
PK 91007 (CF/JF/92-080)	interspecies hepatic metabolism	^{3}H-adapalene	human, mouse, rat, rabbit, dog	cultured hepatocytes	cellular concentration, metabolite profiles
PK 91005 (DCa/JF/92-020)	liberation/ cutaneous penetration	^{14}C-adapalene 0.1% in solution, aqueous gel, cream	human	dermatomised abdominal skin in diffusion cell	distribution in surface excess, epidermis, dermis, receptor medium
TILL/90402 (DC/JF/91-143)	blood and plasma protein binding	^{3}H-adapalene	human	erythrocytes in plasma and in protein solutions	distribution between erythrocyte and specific protein fractions

TABLE 5

BIOPHARMACEUTIC STUDIES SUMMARY TABLE

Study Number (Other identifying report number)	Route of Administration	Dosage Forms(s)/ Study Designs	Dose	Batch Number/ Date Manufactured/ Plant	Number of Subjects	Applicant Conclusion
CIR/271/89001 (DC/JF/91-142)	Epicutaneous	0.1% adapalene solution Single dose, 24h contact period	0.5 mL to 250 cm^2	^{14}C-271/008A/F1 Code S3* February 1989 CIRD GALDERMA, France	4	cutaneous absorption was low
PC 86020 (DC/JF/91-141)	Epicutaneous	0.1% adapalene solution 0.1% adapalene aqueous gel 0.1% adapalene alcoholic gel Single dose, 1 and 24h contact period	50 mg of formulation to 7.5 cm^2 50 mg of formulation to 7.5 cm^2 50 mg of formulation to 7.5 cm^2	524416/F5 Code S3* Nov. 26-27, 1987 524635/2/F1 Code G2* Oct. 14, 1987 524645/F1 Code G4* Aug. 31, 1987 GALDERMA Chevilly, France	12 12 12	greater cutaneous penetration was observed with the gels than with the solution

TABLE 6

Adapalene Detection in Plasma Samples During Clinical Trials With Adapalene Solution

Study	Number of Patients	Test Material	Treatment Duration (Weeks)	Treatment Regimen	Skin Area Treated	Adapalene In Plasma (detection limit)
PC 86012	10	Adapalene Solution 0.1%	8	10 drops twice a day	back (100 cm^2)	ND (1 ng/mL)
PC 86013	1	Adapalene Solution 0.1%	8	10 drops once a day	face (100 cm^2)	ND (1 ng/mL)
PC 86030	10	Adapalene Solution 0.1%	8	10 drops twice a day	face (200 cm^2)	ND (1 ng/mL)
CR 88043	8	Adapalene Solution 0.1%	12	A light film once a day	face + back (200-800 cm^2)	ND (0.15 ng/mL)

ND = Not Detectable

VIII. OVERALL COMMENTS:

1. The analytical methods used in the *in vivo* studies for the assay of adapalene in plasma are acceptable.

2. The *in vitro* studies included in the Pharmacokinetics Section of this submission help to understand i) that interspecies variation exists in the metabolic pathway of adapalene (based on the *in vitro* metabolism of adapalene using cultured hepatocytes of different species including man), ii) that adapalene binds 99% to human whole blood (about 26% to erythrocytes), and iii) that the percentage of adapalene penetration through human skin is formulation dependent (gel>cream>solution). However, data on the metabolism and distribution of adapalene *in vivo* was not provided. The sponsor states that this lack of *in vivo* human data is due to technical limitations.

3. The overall results from the biopharmaceutic and clinical studies included in this NDA indicate that i) a fraction of adapalene was absorbed after single topical administration of 0.1% solution of radiolabeled-adapalene (some traces of radioactivity were found in the feces, but no quantifiable levels in the plasma samples), ii) pharmacokinetic parameters and metabolic profiles could not be generated due to the extremely low detected quantities of adapalene, iii) liberation of adapalene in the stratum corneum (*in vivo*) is formulation dependent (aqueous gel>alcoholic gel>solution), and iv) adapalene was not detected in the plasma samples of acne patients following chronic administration (detection limit of 1 ng/ml).

NOTE: The sponsor rounded the fraction absorbed to 5% for safety considerations.

IX. PROPOSED PACKAGE INSERT

LABELING COMMENTS:(*The proposed Package Insert is included in Attachment VI*)

1. It is recommended that the labeling statement "Absorption of adapalene through human skin is low; in clinical trials measurable plasma levels were not detected following chronic topical application.", included in the Clinical Pharmacology section of the proposed package insert, be modified as follows;

"***The absorption of adapalene through human skin is low. Data from clinical trials where the systemic absorption of adapalene was monitored in acne patients after multiple topical application of 0.1% Differin™ Solution, do not show any measurable plasma levels of adapalene at a detection limit of 1 ng/ml.***"

2. It is recommended to include in the Pharmacokinetic section of the package insert the information obtained in Study No. CIR/271/89001 (Pharmacokinetic and Metabolic Profile of Adapalene after Single Topical Application);

"In a study conducted in four male volunteers following a single topical application of 0.5 ml of a solution containing 0.1% ^{14}C-adapalene did not result in any measurable adapalene plasma levels. However, some traces of radioactivity were found in the feces of each subject mainly between the third and sixth day following the administration. The amount measured accounted for about 0.02-0.06% of the adapalene's administered dose".

3. It is recommended to include in the Pharmacokinetic section of the package insert the information obtained in Study No. TILL/90402 (Blood and Plasma Protein Binding);

"In vitro studies reveled that more than 99% of adapalene was bound in human whole blood. About 26% was bound to erythrocytes with lipoprotein and human serum albumin accounting for the majority of plasma binding".

4. The labeling statement "Excretion appears to be primarily by the biliary route", included in the Clinical Pharmacology section of the proposed package insert should be deleted.

5. Regarding the information included in page 2 0008 of the annotated pachage insert, the doses for the animal:human comparisons are not clear for the discussion of pregnancy effects. The "Pregnancy" part of the Precautions Section of the labeling should be modified as appropriate to clearly indicate the dose comparisons between animal and human data (doses/kg/day used in the animal studies that are equivalent to the expected human daily doses).

CONCLUSION:

For the proposed package insert for Differin™ Solution, it is acceptable, provided the changes that are proposed are incorporated into the *Pharmacokinetic* part of the Clinical Pharmacology section of the package insert.

Angelica Dorantes 9/17/93
Angelica Dorantes, Ph.D.
Pharmacokinetic Evaluation Branch

RD Initialed by Frank Pelsor, Pharm. D. 8/31/93
FT Initialed by Frank Pelsor, Pharm. D. Frank R. Pelsor 9/30/93

Biopharm Day (9/16/93 Collins, Ludden, Hepp, Pelsor, Dorantes)
cc: NDA 20-338, HFD-340 (Vishwanathan), HFD 510, HFD-426 (Fleischer, Pelsor, & Dorantes),Drug, Chron, and HFD-19 (FOI).

Stat

NOV 2 1993

Statistical Review and Evaluation

NDA#: 20-338

Applicant: Owen Galderma Laboratories Inc., Fort Worth, TX 76115

Name of Drug: Differin™ Solution 0.1% (Adapelene Topical Solution)

Documents Reviewed: Volumes 2.1, 2.45 - 2.61, Appendices I, II and III, Amendments dated May 21, 1993 and June 1, 1993.

Indication: Acne Vulgaris

Medical Input: Dr. David Bostwick, HFD-520

A. INTRODUCTION

The sponsor submitted results to establish efficacy and safety profile of a Differin™, 0.1% Adapalene topical solution for treatment of facial acne.

Reports of six controlled clinical trials were submitted by the sponsor, of which three were conducted in U.S and are considered as pivotal studies for efficacy analyses. These three pivotal studies were multi-center, double blinded, randomized, parallel group efficacy trials on patients having acne vulgaris.

Protocols C-88-27 and 9104-CD271-EV were vehicle controlled trials, whereas Protocol C-88-26 was an active-control trial with 0.025% Retin-A gel as comparitor. All three protocols were conducted on a dosing regimen of once a day application for 12 weeks, the Week 12 evaluation serving as the clinical endpoint.

Baseline Consistency:

Table 1. Baseline Consistency for demographic variables

Criteria	Protocol C-88-26	Protocol C-88-27	Protocol 9104-CD271L-EV
Age	p = 0.488[1]	p = 0.783	p = 0.365[1]
Gender	p = 0.771[1]	p = 0.483	p = 0.369[1]
Race	p = 0.134[1]	p = 0.967	p = 0.629[1]
Baseline disease severity	p = 0.853	p = 0.201	p = 0.511

1 : Includes all patients

It is noted that there are no significant differences between treatment arms with respect to age, gender, race or disease severity at baseline. The p-values are obtained from Cochran-

Mantel-Haenszel test or from Chi-square, as appropriate.

In-depth analysis on comparative rates for enrollment, cure, losses and disease severity on a per center basis is addressed in an amendment to this review by Dr. Srinivasan. This is especially helpful in the light of some treatment by center interactions noted in the primary efficacy analyses.

B. EFFICACY EVALUATION

The primary efficacy variables are percent change in total, non-inflammatory and inflammatory lesion counts from baseline and investigator's global assessment scores.

In the sponsor's proposed label (volume 2.1, page 2-0005), they claim that "studies in acne patients provide clinical evidence that topical adapelene is effective in reducing the non-inflammatory acne lesions". They also claim that "studies in human patients provide clinical evidence that topical adapalene is effective in reducing the inflammatory components of acne".

At every visit, investigators assigned a "FDA" grade for global severity assessment of facial acne. This was calculated based on patient's Cunliffe grade as follows:

Cunliffe grade	FDA grade
0.25 - 0.75	I
1.00 - 2.00	II
3.00 - 5.00	III
6.00 - 10.0	IV

In protocol C-88-26, the sponsor used a non-parametric median test for comparing lesion count (open, closed, papules, pustules, nodules, cysts). Comparison of medians is felt not to be adequately informative about the disease resolution and is not reported as a primary analysis. In the same protocol, a transformation was used on the total, non-inflammatory and inflammatory lesion counts for analysis of covariance.

The transformed lesion count = (square root of lesion counts) x mean(square root of lesion counts).

Sponsor claims that this adjusts for skewness in the data, but in reality, this makes detection of any underlying difference in treatment arms harder. No attempt or provision was made to convert results back to original measurement scales. It was also not considered as a part of the primary analysis.

Change from baseline in actual lesion counts is considered in this review for each of the three pivotal studies.

The analyses presented here are based on the sponsor's database.

Protocol 9104-CD271L-EV:

Table 2 summarizes change in lesion count from baseline in Protocol 9104-CD271L-EV.

Table 2: Percent change from baseline lesion counts (Protocol 9104-CD271L-EV)

Week	Reduction	Total lesion			Non-Inflammatory lesion			Inflammatory lesion		
		Diff	vehi	p-val	Diff	vehi	p-val	Diff	vehi	p-val
Week 2	> 75%	1	1		3	3		7	2	
	51-75%	6	6	0.067	8	8	0.054	13	16	0.976
	26-50%	32	24		30	20		17	27	
	<= 25%	58	77		56	77		60	63	
Week 4	> 75%	1	2		4	4		8	5	
	51-75%	16	16	0.238	13	15	0.083	16	22	0.928
	26-50%	39	39		44	28		29	31	
	<= 25%	47	63		42	64		50	53	
Week 8	> 75%	6	6		9	7		16	15	
	51-75%	32	20	0.001*	31	16	0.000*	31	19	0.085
	26-50%	33	21		33	23		18	22	
	<= 25%	28	58		26	59		34	49	
Week 12	> 75%	10	8		13	8		18	15	
	51-75%	28	18	0.021*	29	23	0.020*	26	25	0.177
	26-50%	23	24		20	20		21	23	
	<= 25%	34	55		33	54		30	42	

Table 2 shows that a statistically significant difference is detected from Week 8 on between Differin and its vehicle in reduction of both total and non-inflammatory lesion counts. It is to be noted that when compared to its vehicle, Differin fails to establish a statistically superior therapeutic profile for inflammatory lesions.

Global assessment analysis for protocol 9104-CD271L-EV is summarized in Table 3:

Table 3: Investigator's Global Assessment Analysis (Protocol 9104-CD271L-EV)

Week	Differin grades				vehicle grades				p-value
	Total	I	II	III	Total	I	II	III	
Week 2	86	15	66	5	95	8	78	9	0.084
Week 4	89	28	57	4	97	21	70	6	0.164
Week 8	86	43	43	-	94	27	61	6	0.001
Week 12	81	36	45	-	91	24	62	5	0.005

Note: The p-values are based on Cochran-Mantel-Haenszel scores controlling for investigators.

This shows that from Week 8, Differin is statistically superior

to its vehicle (p-value < 0.05). The findings corroborate table 2.

Results of this study fail to support the sponsor's proposed claim of effectiveness in treatment of inflammatory and non-inflammatory lesions.

Protocol C-88-26:

We now consider Protocol C-88-26, an active control study of Differin 0.1% Lotion against 0.025% Retin-A gel. Table 4 summarizes the change from baseline in lesion counts.

Table 4: Percent change from baseline lesion count (Protocol C-88-26)

Week	Reduction	Total lesion			Non-Inflammatory lesion			Inflammatory lesion		
		Diff	Retin-A	p-val	Diff	Retin-A	p-val	Diff	Retin-A	p-val
Week 2	> 75%	1	0		2	6		3	5	
	51-75%	12	11	0.694	17	13	0.223	12	12	0.610
	26-50%	38	41		41	30		36	35	
	<= 25%	71	82		62	85		71	82	
	TOTAL	122	134		122	134		122	134	
Week 4	> 75%	5	4		6	14		8	9	
	51-75%	23	26	0.882	26	19	0.896	23	30	0.967
	26-50%	39	46		38	39		38	37	
	<= 25%	56	59		53	63		54	59	
	TOTAL	123	135		123	135		123	135	
Week 8	> 75%	11	12		18	16		16	11	
	51-75%	42	44	0.546	37	48	0.719	41	38	0.059
	26-50%	38	39		34	26		21	28	
	<= 25%	21	32		23	37		34	50	
	TOTAL	112	127		112	127		112	127	
Week 12	> 75%	25	15		36	22		18	23	
	51-75%	40	56	0.279	28	46	0.128	46	40	0.646
	26-50%	27	32		28	32		21	37	
	<= 25%	19	23		19	26		26	26	
	TOTAL	111	126		111	126		111	126	

Table 4 shows that for all observation points, Differin 0.1% Lotion and Retin-A 0.025% gel are therapeutically equivalent (p-value > 0.05) in reducing total, non-inflammatory and inflammatory lesion counts. It is to be noted that there is some variability in number of evaluable patients over visits.

Investigator's global assessment corroborates therapeutic equivalence of Differin .1% Lotion with Retin-A 0.025% gel. The results are presented in the Table 5:

Table 5: Investigator's Global Assessment Analysis
(Protocol C-88-26)

Week	Differin grades				Retin-A grades				p-value
	Total	I	II	III	Total	I	II	III	
Week 2	122	13	103	6	133	18	108	7	0.261
Week 4	123	30	88	5	135	29	102	4	0.897
Week 8	112	40	70	2	126	44	81	1	0.964
Week 12	110	53	56	1	126	61	63	2	0.714

Note: The p-values are based on Cochran-Mantel-Haenszel scores controlling for investigators.

Table 5 indicates that Differin is therapeutically equivalent to Retin-A with respect to investigator's global assessment analysis at every visit, including the clinical endpoint at Week 12. The investigator's impression of whether acne improved by week 12 is reported to have a p-value of 0.854, which corroborates the findings (volume 2.58, page 8-4937).

Protocol C-88-27:

Protocol C-88-27 is a vehicle-controlled trial. Table 6 summarizes percent change from baseline for total, non-inflammatory and inflammatory lesion counts.

Table 6: Percent change from baseline lesion count
(Protocol C-88-27)

Week	Reduction	Total lesion			Non-Inflammatory lesion			Inflammatory lesion		
		Diff	vehi	p-val	Diff	vehi	p-val	Diff	vehi	p-val
Week 2	> 75%	0	0		0	0		1	3	
	51-75%	6	3	0.481	10	6	1.000	9	5	0.280
	26-50%	10	12		5	13		15	10	
	<= 25%	33	33		34	29		24	30	
	TOTAL	49	48		49	48		49	48	
Week 4	> 75%	2	1		2	2		3	3	
	51-75%	9	11	0.250	11	12	0.153	7	13	0.616
	26-50%	7	14		5	14		15	11	
	<= 25%	31	21		31	19		24	20	
	TOTAL	49	47		49	47		49	47	
Week 8	> 75%	2	1		2	4		3	4	
	51-75%	10	10	0.591	13	10	0.945	14	13	0.405
	26-50%	11	14		6	11		9	7	
	<= 25%	21	21		23	21		18	22	
	TOTAL	44	46		44	46		44	46	
Week 12	> 75%	8	2		9	3		12	7	
	51-75%	14	18	0.046*	12	15	0.038*	11	17	0.265
	26-50%	9	9		11	12		12	10	
	<= 25%	13	17		12	16		9	12	
	TOTAL	44	46		44	46		44	46	

Table 6 shows that for all visits except Week 12, Differin 0.1% Lotion fails to establish therapeutic superiority over vehicle (p-value > 0.05) in reducing total, non-inflammatory and inflammatory lesion counts. At Week 12, which is the clinical endpoint, Differin

is superior to vehicle in reduction of total and non-inflammatory lesions and equivalent to vehicle in reduction of inflammatory lesions.

Protocol C-88-27 is analyzed in Table 7 with respect to investigator's global assessment score.

Table 7: Investigator's Global Assessment Analysis (Protocol C-88-27)

Week	Differin grades					vehicle grades					p-value
	Total	clear	I	II	III	Total	clear	I	II	III	
Week 2	49	--	9	40	--	47	--	13	31	3	0.359
Week 4	49	--	15	34	--	46	--	21	24	1	0.125
Week 8	44	1	22	21	--	45	1	20	22	2	0.727
Week 12	44	--	31	13	--	46	1	27	16	2	0.415

Note: The p-values are based on Cochran-Mantel-Haenszel scores controlling for investigators.

Table 7 indicates that Differin fails to establish a therapeutic superiority to its vehicle with respect to investigator's global assessment analysis at every visit, including the clinical endpoint at Week 12. The investigator's impression of whether acne improved by week 12 is reported to have a p-value of 0.198, which corroborates the findings (volume 2.47, page 8-0748).

It is to be pointed out that for the Protocol C-88-27, the sponsor noted in volume 2.1, page 2-0243, paragraph 2 that "the pooled data showed both adapelene 0.1% solution and vehicle were minimally effective though not statistically significant in reducing acne lesions when overall changes in lesion counts and global ratings were analyzed". In the efficacy summary in volume 2.1, page 2-0271 the sponsor reiterated that for percent change in lesion counts from baseline to Week 12 evaluation visit "shows numerical differences in favor of adapelene solution but statistical significance was not achieved when analysis of covariance was performed".

Analysis of secondary variables is not attempted since Differin fails to establish an uniformly superior therapeutic profile over its vehicle.

Longitudinal data analysis is not attempted since no serial correlation is believed to be present in the primary efficacy variables.

B. SAFETY EVALUATION

An integrated safety analysis is provided here. This includes pivotal studies C-88-27, 9104-CD271-EV and C-88-26 conducted in U.S., studies PC-86-030, PH-87-027 and CR-88-043 conducted in Europe; supportive studies PC-86-019, PC-86-013 and PC-86-012 and open label extensions to pivotal studies C-88-27 and C-88-27.

Table 8 and 9 summarize the adverse clinical reactions reported that are related or possibly related to the test drug. There were no adverse laboratory reaction reported. Dermatologic events are analyzed first, followed by non-dermatologic events.

Any adverse reaction that has 1% or higher incidence rate in the exposed population is reported in this analysis.

Table 8: Summary of Adverse Dermatologic Events

Adverse Effect	Differin (N=571)	Retin-A gel (N=281)	Differin vehicle (N=223)	95% Confidence Interval n_1, n_2 (95% C.I.) p_1, p_2
Skin discomfort (burning and stinging)	21	4	2	Differin vs Retin-A: $_{571,281}$ (-.0008, .0459) $_{3\%,1\%}$ Differin vs vehicle: $_{571,223}$ (.0049, .0507) $_{3\%,0.8\%}$
Skin irritation	14	5	1	Differin vs Retin-A: $_{571,281}$ (-.0159, .0293) $_{2\%,1\%}$ Differin vs vehicle: $_{571,223}$ (.0114, .0531) $_{2\%,0.4\%}$
Erythema	12	2	0	Differin vs Retin-A: $_{571,281}$ (-.0040, .0318) $_{2\%,0.7\%}$ Differin vs vehicle: $_{571,223}$ (.0061, .0538) $_{2\%,0\%}$
Dry skin	11	2	0	Differin vs Retin-A: $_{571,281}$ (-.0054, .0297) $_{1\%,0.7\%}$ Differin vs vehicle: $_{571,223}$ (.0048, .0336) $_{1\%,0\%}$
Pruritus	8	1	3	Differin vs Retin-A: $_{571,281}$ (-.0040, .0249) $_{1\%,0.3\%}$ Differin vs vehicle: $_{571,223}$ (-.0204, .0216) $_{1\%,1\%}$

This shows that Differin is statistically equivalent to Retin-A gel with respect to incidence of skin irritation and discomfort, erythema, pruritus and dry skin. It has significantly higher incidence rate than its vehicle with respect to each of these symptoms except pruritus.

Table 9 discusses the non-dermatologic adverse events having 1% or higher incidence rate in the exposed population.

Table 9: Summary of Adverse Non-dermatologic Events

Adverse Effect	Differin (N=571)	Retin-A gel (N=281)	Differin vehicle (N=223)	95% Confidence Interval n_1, n_2 (95% C.I.) p_1, p_2
Cold syndrome	24	8	3	Differin vs Retin-A: $_{571,281}$ (-.0145, .0416) $_{4\%,2\%}$ Differin vs vehicle: $_{571,223}$ (.0031, .0540) $_{4\%,1\%}$
Headache	13	2	18	Differin vs Retin-A: $_{571,281}$ (-.0026, .0339) $_{2\%,0.7\%}$ Differin vs vehicle: $_{571,223}$ (-.0988, -.0170) $_{2\%,8\%}$
Flu syndrome	12	8	9	Differin vs Retin-A: $_{571,281}$ (-.[illegible]128, .0179) $_{2\%,2\%}$ Differin vs vehicle: $_{571,223}$ (-.0508, .0121) $_{2\%,4\%}$
Pharyngitis	8	5	1	Differin vs Retin-A: $_{571,281}$ (-.0246, .0170) $_{1\%,1\%}$ Differin vs vehicle: $_{571,223}$ (-.0066, .0256) $_{1\%,0.4\%}$
Rhinitis	7	2	1	Differin vs Retin-A: $_{571,281}$ (-.0108, .0211) $_{1\%,0.7\%}$ Differin vs vehicle: $_{571,223}$ (-.0079, .0234) $_{1\%,0.4\%}$
Dysmenorrhea	7	1	3	Differin vs Retin-A: $_{571,281}$ (-.0053, .0227) $_{1\%,0.3\%}$ Differin vs vehicle: $_{571,223}$ (-.0219, .0195) $_{1\%,1\%}$

Significant difference in incidence rates are observed only between Differin and its vehicle with respect to cold syndrome. Significantly lower incidence rates are observed for headache in Differin over its vehicle. with respect to cold and flu syndrome, pharyngitis, rhinitis or dysmenorrhea, there is no statistically significant difference between the treatment arms.

Whether these are clinically meaningful or not needs to be assessed by the medical officer.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

Of the two vehicle-controlled studies (protocols 9104-CD271L-EV and C-88-27), Differin is therapeutically superior to its vehicle in protocol 9104-CD271L-EV and statistically equivalent to its vehicle in protocol C-88-27 with respect to percent reduction of total and non-inflammatory lesion count from baseline at Week 12 visit (tables 2 and 6). It fails to establish a statistically superior therapeutic profile with respect to percent reduction of inflammatory lesion counts from baseline at Week 12 visit (tables

2 and 6) in both vehicle-controlled studies. Neither of the vehicle control trials support the sponsor's proposed label claims of effectiveness in treatment of inflammatory and non-inflammatory lesions (tables 2 and 6).

Differin fails to establish a statistically superior therapeutic profile to vehicle in investigator's global assessment scores except in Protocol 9104-CD271L-EV at Week 8 and 12 visits (tables 3, 5 and 7).

Differin is statistically equivalent to Retin-A gel in reduction of total, non-inflammatory and inflammatory lesions (protocol C-88-26, table 4).

This corroborates the sponsor's findings.

Differin is statistically equivalent to Retin-A gel with respect to incidence of skin irritation and discomfort, erythema, pruritus and dry skin. It has significantly higher incidence rate than its vehicle with respect to each of these symptoms except pruritus (tables 8 and 9).

These trials fail to support the sponsor's efficacy claims as stated in their proposed label.

Alaka Chakravarty 10/29/93
Alaka G. Chakravarty, Ph.D.
Biomedical Statistician, Group 7

Ralph Harkins, Ph.D.
Concur: Ralph Harkins, Ph.D. 10/29/93

Satya D. Dubey, Ph.D. 11-1-93

cc:
Orig. NDA 20-338
HFD-520
HFD-520/Ms. Rosemary Cook
HFD-520/Dr. Gavrilovich
HFD-520/Dr. Bostwick
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-713/Dr. Chakravarty
HFD-344/Dr. Lisook
Chron.

This review contains 9 pages.

11/9/93

Statistical Review and Evaluation
Amendment

NDA#: 20-338

Applicant: Owen Galderma Laboratories Inc., Fort Worth, TX, 76115

Name of Drug: Differin™ Solution 0.1% (Adapalene Topical Solution)

Documents Reviewed: Additional analyses submitted by the company for the Study 9104-CD271L-EV

Indication: Acne Vulgaris

Medical Input: David Bostwick, HFD-520

1. Introduction: The clinical reviewer, Mr. David Bostwick requested the company to do further analyses of the Study 9104-CD271L-EV without Dr. Hickman's data. Table 1 is extracted from the sponsor's analysis of square root of total lesion counts at Week 12 and End-Point for patients evaluable for efficacy. In the original statistical review and evaluation of Differin, it was noted that use of the square root transformation did not impact the conclusions derived from these data. The sponsor's proposed label claims that Adapalene is effective for treatment of both inflammatory and non-inflammatory lesions.

Table 1

Protocol 9104-CD271-L-EV
Efficacy evaluation of 0.1% CD271 Lotion Versus CD271 Lotion Vehicle

Analysis of square root of total lesion counts at Week 12 and End-Point
Includes only patients evaluable for efficacy

Model	N(CD 271L)(Mean/Std)*	N(VEHICLE)(Mean/Std)*	P(TRT.)	P(INV.)	P(TRT X INV)
Original Submission					
Week 12	95(51.5/39.1)	105(68.5/56.4)	0.0171	0.0001	0.0201
End-Point	102(53.3/44.1)	112(71.7/57.0)	0.0336	0.0001	0.0352
Without Hickman					
Week 12	83(47.8/37.0)	96(59.7/45.6)	0.0390	0.0001	0.1050
End-Point	89(50.4/43.4)	92(63.3/48.2)	0.0863	0.0001	0.0127
Without Ast					
Week 12	95(50.9/40.7)	96(69.2/54.9)	0.0010	0.0001	0.2000
End-Point	92(52.9/46.0)	103(71.7/55.8)	0.0023	0.0001	0.3344
Without Hickman and Ast					
Week 12	73(46.8/38.7)	77(58.2/41.6)	0.0017	0.0001	0.0772
End-Point	79(49.6/45.5)	83(62.3/45.2)	0.0068	0.0001	0.1809

*(Mean/Std) of the Non-Inflammatory Lesion Counts

The results of the sponsor's statistical analyses in Table 1, without Dr. Hickman's data, revealed similar results to the analysis in the original submission. Adapalene was statistically better than Vehicle at Week 12 ($p=0.0380$) and marginally statistically significant at End-Point ($p=0.0853$). However, the treatment by investigator interaction remained statistically significant at both visits (Week 12, $p=0.0050$; End-Point, $p=0.0127$) with Dr. Hickman's data removed. Figure 1 contains a plot of each investigator at End-Point and it indicates that Dr. Ast's data is the cause of the significant treatment by investigator interaction. An analysis without Dr. Ast's data revealed that the significant interaction was removed (Week 12, $p=0.2000$; Endpoint, $p=0.3344$) and that the treatment effect showed that Adapalene was statistically better than Vehicle at Week 12 ($p=0.0010$) and End-Point ($p=0.0023$). The analysis with both Dr. Hickman's and Dr. Ast's data removed revealed that the significant interaction was removed (Week 12, $p=0.0772$; End-Point, $p=0.1809$) and the Adapalene was statistically better than Vehicle at Week 12 ($p=0.0017$) and End-Point ($p=0.0058$).

Table 2 is extracted from the sponsor's analysis of square root of non-inflammatory lesion counts at Week 12 and End-Point for patients evaluable for efficacy.

Table 2

Protocol 8104-CD271L-EV
Efficacy evaluation of 0.1% CD271 Lotion Versus CD271 Lotion Vehicle
Analyses of square root of non-inflammatory lesion counts at Week 12 and End-Point
Includes only patients evaluable for efficacy

Model	N(CD271L)(Mean/Std)*	N(VEHICLE)(Mean/Std)*	P(TRT.)	P(INV.)	P(TRT X INV)
Original Submission					
Week 12	95(38.7/30.7)	105(55.5/53.3)	0.0050	0.0001	0.0200
End-Point	102(40.1/36.7)	112(57.6/53.9)	0.0090	0.0001	0.0270
Without Hickman					
Week 12	83(34.6/27.3)	86(45.2/40.9)	0.0149	0.0001	0.0064
End-Point	89(37.0/35.3)	92(48.5/43.9)	0.0317	0.0001	0.0114
Without Ast					
Week 12	95(37.9/31.7)	96(55.6/51.6)	0.0001	0.0001	0.3912
End-Point	92(39.6/38.1)	103(57.9/52.4)	0.0002	0.0001	0.5199
Without Hickman and Ast					
Week 12	73(33.1/27.8)	77(44.1/38.1)	0.0004	0.0001	0.2244
End-Point	79(35.9/36.7)	83(47.8/40.2)	0.0009	0.0001	0.3735

*(Mean/Std) of the Total Lesion Counts

Table 2 shows that Adapalene was statitically better than Vehicle at Week 12 and End-Point with all investigators included ($p<0.0090$), with Dr.Hickman removed ($p<0.0317$), with Dr. Ast removed ($p<0.002$), and with Dr. Hickman and Dr. Ast removed ($p<0.0009$). The statistically significant treatment by investigator interaction was non-

significant when Dr. Ast was removed and remained significant when only Dr. Hickman was removed.

The sponsor's analyses of Inflammatory Lesions showed that Adapalene was not statistically better than Vehicle at Week 12 or End-Point for any model considered ($p>0.05$). For Cunliffe global assessment, Adapalene was statistically better than Vehicle at Week 12 and End-Point for all models considered ($p<0.05$).

2. Conclusions: The sponsor's supplemental analyses of the Study 9104-CD-271L-EV provide evidence to support the sponsor's claim that Adapalene Topical Solution (**Differin™ Solution 0.1%**) is statistically better (Tables 1 and 2) than Vehicle in the treatment of Acne Vulgaris for **non-inflammatory but, not for inflammatory lesions.**

The reviewer found that the demographic variables, loss rates by investigator, total lesion counts, non-inflammatory lesion counts and inflammatory lesion counts at baseline for the individual investigators exhibit no imbalance across the investigators and hence the statistical analyses done by the sponsor after dropping the investigators, Dr. Ast and Dr. Hickman, is not justifiable.

The sponsor's proposed label states Adapalene Solution is effective for treatment of both non-inflammatory and inflammatory lesions. However, the supplemental analyses of the Study 9104-CD-271L-EV fail to be support the sponsor's claim.

R.Srinivasan, Ph.D.
Mathematical Statistician (Biomedical)

Concur: Dr. Ralph Harkins 18/9/93

Dr. Satya Dubey 11-9-93

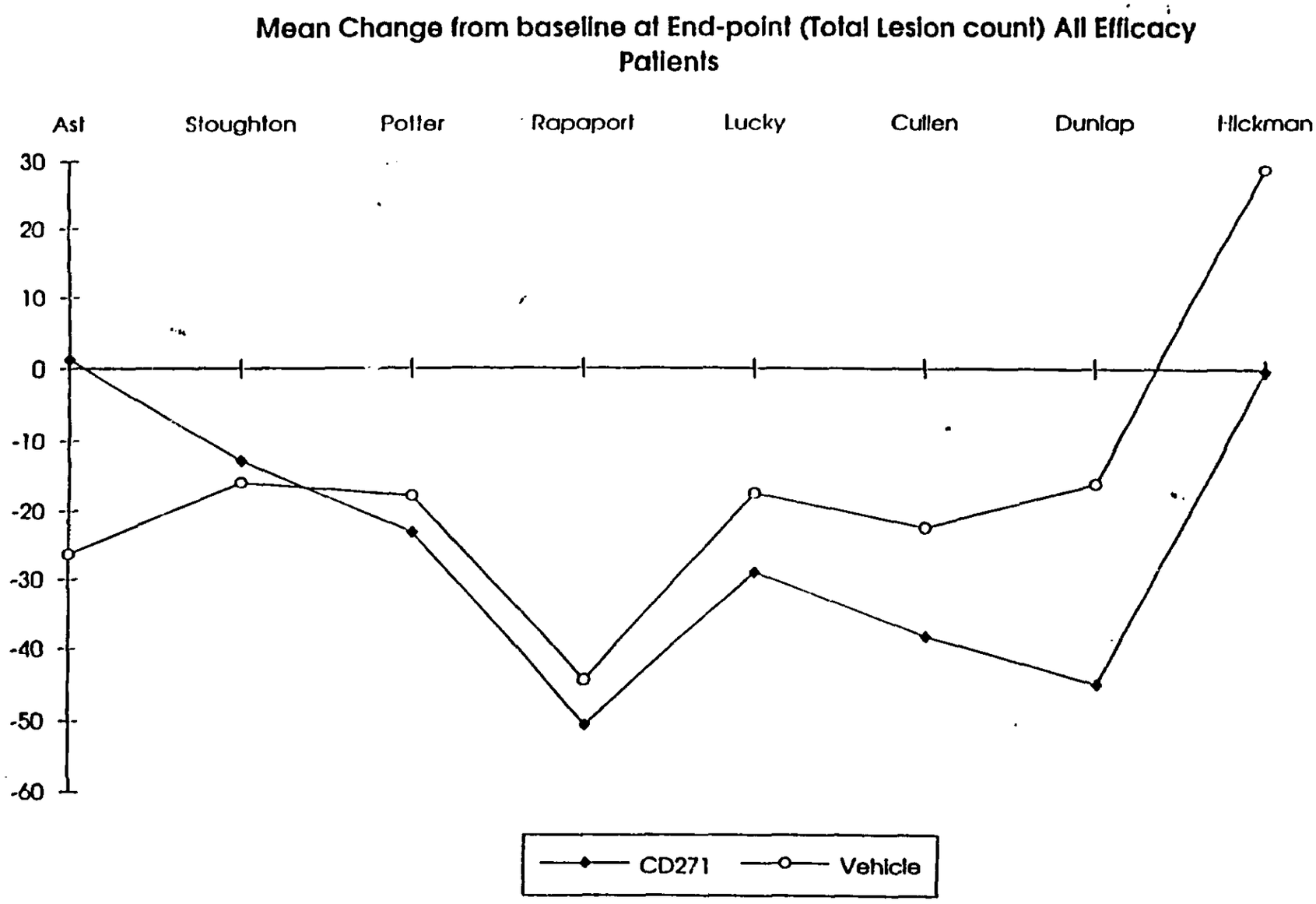
cc:
Orig. NDA 20-338/Amendment
HFD-520
HFD-520/Ms. Rosemary Cook
HFD-520/Dr. Gavrilovich
HFD-520/Dr. Bostwick
HFD-713/Dr. Dubey [File DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-713/Dr. Srinivasan
HFD-344/Dr. Lisook
Chron.

This amendment contains 4 pages.

Srinivasan/10/29/93/X4710/WPTEXT/C:\REVIEWS.NDA\ADAPALENE.SOL

Figure 1

Protocol 9104-CD-271L-EV



M E M O R A N D U M

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

Date: July 12, 1994

From: Alaka G. Chakravarty, Ph.D.
Biomedical Statistician,
SERB (HFD-713)

Subject: NDA 20-338 (Differin 1% Solution)

To: Ms. Rosemary Cook,
Acting Supervisory CSO, HFD-540

I reviewed the consult request you sent on 6-3-94 regarding labelling and package insert of Differin 1% solution.

In the ADVERSE REACTIONS section of the package insert, the frequent adverse reactions (occuring in more than 1% of the exposed population) and their respective percentage of occurrence agree with Table 8 of my statistical evaluation of safety dated Nov 2, 1993.

The proposed labelling is acceptable from a statistical perspective.

Alaka Chakravarty 7/12/94
Alaka G. Chakravarty, Ph.D.

cc:

Chron.
HFD-540/ Dr. Wilkin
HFD-520/ Mr. Bostwick
HFD-520/ Dr. Chakravarty
HFD-713/ Dr. Harkins
HFD-713/ Dr. Dubey [File: DRU 1.3.1]

Statistical Review and Evaluation

NDA #: 20-338 Date: APR 15 1994

Applicant: Owen/Galderma Laboratories, Inc.

Name of Drug: Adapalene Topical Solution (Differin Solution 0.1%)

Documents Reviewed:

1. NDA submission volume 2.8 to 2.10, "Study Report MD/92069 (Toxicity phase) 78-week chronic toxicity study by dietary administration of CD 271 to CD rats.", Report Date: April 13, 1992.

2. NDA submission volume 2.17 to 2.24, "Study Report MD/92071 CD 271: Aqueous Gel Suspension: oncogenicity study by topical application to CD-1 mice for their life span.", Report Date: March 30, 1992.

3. NDA submission volume 2.25 to 2.30, "Study Report MD/92070 CD 271: Combined oncogenicity and toxicity study by dietary administration to CD rats for 104 weeks: oncogenicity phase.", Report Date: April 13, 1992.

4. NDA Special Submission, Date of Document, March 10, 1994, Data Diskettes for two animal tumorigenicity studies and one toxicity study.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) and one 78-week rat toxicity study were included in this NDA submission. The purpose of these study was to assess the toxicity and oncogenicity of the test material, CD 271 (Adapalene Topical Solution), when given by dietary administration to Charles River CD rats and by topical application to Charles River mice for 78 to 104 weeks. Dr. Kumar D. Mainigi, HFD-520, who is the reviewing pharmacologist of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of these three studies. The data submitted on computer floppy diskettes were used in the reviewer's independent analyses.

II. The Rat Study

II. a. Design

CD 271 active ingredient was tested at in a combined oncogenicity and toxicity studies by dietary administration to CD rats for 104 weeks. The in-life chronic toxicity phase of this study was conducted from April 1989 to October 1990. The oncogenicity phase of this study was conducted from April

1989 to April 1991.

In the 78-week chronic toxicity phase, groups of 20 male and 20 female CD rats received CD 271 continuously via the diet at doses of 0.15, 0.5 or 1.5 mg/kg/day. A similarly constituted control group received untreated diet. An additional ten male and ten female rats were assigned to each group in a satellite study, solely for proof of absorption and blood chemistry investigations. In the 104-week oncogenicity phase, groups of 60 male and 60 female CD rats received CD 271 continuously via the diet at dosages of 0.15, 0.5 or 1.5 mg/kg/day. A similarly constituted control group received untreated diet.

The following table lists three design phases with the animal identity numbers:

Oncogenicity Phase:

Group	Treatment	Dosage (mg/kg/day)	Animal Numbers Male	Female
1	Control	0		
2	CD 271	0.15		
3	CD 271	0.50		
4	CD 271	1.50		

Toxicity Phase:

Group	Treatment	Dosage (mg/kg/day)	Animal Numbers Male	Female
1	Control	0		
2	CD 271	0.15		
3	CD 271	0.50		
4	CD 271	1.50		

Satellite Phase:

Group	Treatment	Dosage (mg/kg/day)	Animal Numbers Male	Female
1	Control	0		
2	CD 271	0.15		

3	CD 271	0.50
4	CD 271	1.50

The animals were inspected at least twice daily for evidence of reaction to treatment or ill-health. A more detailed weekly examination, which included palpation, was performed on each animal. Food consumptions were recorded for each week throughout the treatment period. Body weights were recorded weekly for the first 14 weeks of treatment, once fortnightly thereafter and before necropsy. All animals killed and any found dead were subjected to a detailed necropsy. For animals on oncogenicity phase, selected tissues were examined microscopically from all rats. For animals on toxicity phase, microscopic examination was performed as follows: (1) selected tissues were examined for all rats of groups 1 and 4 sacrificed on completion of the scheduled treatment period and for all rats killed or dying during the study, (2) adrenal, bone, kidneys, liver, spleen and testes from all animals of groups 2 and 3, (3) tissues reported at macroscopic examination as being abnormal were examined for all rats.

II. b. Sponsor's Analyses on 104-week Oncogenicity Phase

Inter-group differences in mortality were analyzed by Cox's proportional hazards model (Cox, D.R., "Regression Models and life-tables", J.R. Stat. Soc. B, 34, 187-220, 1972) and Tarone's partition of the chi-square statistic into linear trend on dose and deviation from linearity (Tarone, R.E., "Tests for Trend in life table analysis", Biometrika, 62, 679-682, 1975). These tests are two-tailed, although the results of a one-tailed trend test are also quoted. Adjusted mortality rates have been estimated using Kaplan-Meier or Product Limit estimations ("Nonparametric estimation from incomplete observations", Journal of the American Statistical Association, 53, 457-481, 1958). These rates are adjusted to account for animals which were censored and therefore whose week of death is unknown. Two analyses were performed. In one analysis, humane kills were taken as censored observations, while in the other analysis they were taken as uncensored. Statistical analysis of mortality revealed no significant inter-group differences or trends for either sex. Tables 1-4 and Figures 1-4 listed the above results.

Fisher's Exact probability test was applied as a two-tailed test, where appropriate, to the distribution of macroscopic or microscopic (non-neoplastic) pathological entities. For the distribution of neoplastic microscopic pathological entities, a one-tailed test was applied to apparent increases in incidence with treatment.

The test results showed that there was a statistically significant higher incidence of benign pheochromocytoma in the adrenal medulla of males which received 1.5 mg/kg/day when compared with the control group. There was no evidence of any effect on the incidence of

malignant pheochromocytomas. The apparently higher incidence of focal hyperplasia among high dose females did not achieve statistical significance. There was no effect on tumor incidence in females. Table 5 listed the incidences of pheochromocytoma among male CD rats from 104-week oncogenicity studies conducted at 1986 and 1987. The sponsor indicated that the higher incidence of pheochromocytoma in male rats treated at 1.5 mg/kg/day than in the controls was not unexpected as rats treated with retinoids, namely retinol acetate and isoretinoin, also known as accutane and 13-cis retinoic acid, have shown similar changes. It is believed that the change may relate to a disturbance of calcium metabolism. It is not, however, considered to provide evidence that CD 271 is a risk to man.

Although the incidences of islet cell tumors of the pancreas were higher in all treated male groups, compared with the controls, statistical significance was not achieved. Table 6 listed the historical control data and the incidences of pancreatic islet cell tumors in male rats.

When benign and malignant follicular cell tumors of the thyroids were combined, their incidence was significantly higher in females which received 1.5 mg/kg/day than in the controls. Table 7 listed the historical control data and the incidences of follicular cell tumors in female rats. The sponsor claimed that this statistical significance was probably due to the unusual zero incidence in the controls. This zero incidence of thyroid follicular cell tumors was only observed in one of the six control studies in the historical control data. The incidence of this tumor in high dose females (8%) was within the range previously observed (0% - 12%).

Based on the above test results, the sponsor concluded that "dietary administration of CD 271 to male CD rats at a dosage of 1.5 mg/kg/day for two years resulted in a higher incidence, relative to the controls, of benign pheochromocytoma of the adrenal medulla. This finding was not unexpected as it has been observed in previous studies on other compounds with retinoid-like activity in the rat. It is not considered to be of significance to man."

II. c. <u>Sponsor's Analyses on 78-week Toxicity Phase</u>

In this study, no statistical analysis was performed on survival data. Table 8 listed the cumulative mortality for each group and sex of this study. Based on these data, the sponsor stated that the group distribution of deaths was considered to be unaffected by treatment.

Similar to the 104-week oncogenicity phase, Fisher's Exact probability test was applied to the tumor data. The results showed that the incidences of benign and malignant pheochromocytomas of the adrenal in males were significant higher in high dose group than in the control group for animals sacrificed after 78 weeks of treatment. When all animals were considered together, the higher incidences of

benign and malignant pheochromocytomas of the adrenal in high dose males were no longer statistically significant. The incidence of adrenal medullary hyperplasia was also higher among male animals receiving the highest dosage than among the controls, but statistical significance was not achieved. There were no inter-group differences with respect to proliferative lesions of the adrenal for females. The sponsor mentioned that as it was uncommon for to conduct 78-week chronic toxicity studies in the CD rat, and that no directly relevant historical control data was available. The sponsor compared the data from this study with historical control data from six 104-week oncogenicity studies (see Table 5), and claimed that the incidences of benign pheochromocytoma among control male (10%) were towards the lower end of the range observed for controls in the previous 104-week studies (8-22%).

Based on the above test results, the sponsor concluded that "the treatment of rats with CD 271 at a dosage of 0.15, 0.5 or 1.5 mg/kg/day for 78 weeks resulted in a number of treatment-related changes. The only neoplastic change was in the adrenal medulla of males which had received 1.5 mg/kg/day. Other changes observed included alterations in the cellular and chemical composition of the blood of males and females. All of the changes are similar to those observed in previous studies on other retinoids in the rat."

II.d. Reviewer's Analyses and Comments on 104-week Oncogenicity Phase

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart ("Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) were used to test for heterogeneity in survival distributions. The p-values of the Cox test were 0.2031 and 0.4478 for males and females, respectively. Hence, there was no statistically significant difference (at 0.05 level) in the survival distribution in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.1258 and 0.2659 for males and females, respectively.

The intercurrent mortality rates for both male and female rats (see Table 9) were tested for linear trend according to the death rate method described in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980). The time intervals used in this method are 0-50, 51-80, and 81-104 weeks. The actual dose levels 0, 0.15, 0.5, and 1.5 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in either female ($p = 0.3667$) or male rats ($p = 0.4869$). Noted that the above analyses were based on the data from the sponsor's submitted diskettes. The

data of humane kills animals were treated as uncensored observations.

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in thyroids follicular cell tumor (p = 0.0049) in female rats. Noted that the sponsor combine both thyroids follicular cell adenoma and carcinoma together in the submitted diskettes. There was a significant (at 0.05 level) positive linear trend in adrenal benign and malignant pheochromocytomas (p = 0.0051) in male rats. There were marginally significant positive linear trends in H'poietic histiocytic sarcoma (p = 0.0696) and in H'poietic monocytic leukaemia (p = 0.0696) in male rats. The incidence rates of the above tumor types are given in Tables 10 to 13.

As mentioned previously, not all tissues of all animals were examined microscopically, the sponsor listed the tumor incidences and number of animals evaluated for each tumor types (see Appendix I). Due to the constraint of the format of the data sent by the sponsor, the above analyses are assumed that all of animals are examined microscopically for selected tumor/organ types. For example, there are 60, 59, 60, and 60 female rats were examined microscopically for thyroids in control, low, medium, and high dose groups. However, the reviewer assumed that there are 60 females for each group were examined microscopically for thyroids.

II.e. Reviewer's analyses and Comments on 78-week Toxicity Phase

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart (1977) were used to test for heterogeneity in survival distributions. The p-values of the Cox test were 0.314 and 0.7147 for males and females, respectively. Hence, there was no statistically significant difference (at 0.05 level) in the survival distribution in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.2947 and 0.7333 for males and females, respectively.

The intercurrent mortality rates for both male and female rats (see Table 14) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980). The time intervals used in this method are 0-50 and 51-78 weeks. The actual dose levels 0, 0.15, 0.5, and 1.5 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in either female (p = 0.1914) or male rats (p = 0.2055).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in

adrenal benign and malignant pheochromocytomas (p = 0.0003) in male rats. The incidence rates of this tumor are given in Tables 15. Noted that there are only 20 animals per sex/group in this study.

II.f. Reviewer's Analyses and Comments on Combined 104-week Oncogenicity and 78-week Toxicity Studies

The reviewer also analyzed the combined survival and tumor data of oncogenicity and toxicity studies.

The intercurrent mortality rates for both male and female rats (see Table 16) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980). The time intervals used in this method are 0-50, 51-78, 79, and 80-104 weeks. The actual dose levels 0, 0.15, 0.5, and 1.5 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in either female (p = 0.3151) or male rats (p = 0.497).

Tumor data analyses showed that there was a significant (at 0.05 level) positive linear trend in thyroids follicular cell adenoma and carcinoma (p = .0017) in female rats. There was a significant (at 0.05 level) positive linear trend in adrenal benign and malignant pheochromocytomas (p < 0.0001) in male rats. There were marginally significant positive linear trends in H'poietic histiocytic sarcoma (p = 0.0605) and in H'poietic monocytic leukaemia (p = 0.0853) in male rats. The incidence rates of the above tumor types are given in Tables 17 to 20.

III. The Mouse Study

III. a. Design

In this study, groups of 50 male and 50 female CD-1 mice received CD 271 aqueous gel suspension, by topical application to the clipped dorsum, at dose levels of 0, 0.03, 0.1, and 0.3% w/w at a volume dosage of 2 mL/kg bodyweight corresponding to 0, 0.6, 2.0, and 6.0 mg/kg/administration respectively. A similarly constituted reference group received the vehicle gel alone at the same frequency as the treated groups. A further similarly constituted group received no treatment and was clipped only. For the first 19 weeks of treatment, the aqueous gel formulations were applied seven times a week. However, on account of the severity of signs observed at the application site of animals treated with CD 271 aqueous gel, the frequency of application was reduced to five times a week. For similar reasons the frequency of application was further reduced to three occasions each week from week 63. For males and females of the high dosage group treatment continued for 98 and 101 weeks respectively. The remaining groups were treated for 104 weeks. An additional 20 male and 20 female mice were assigned to each group

receiving CD 271 aqueous gel and to the group receiving the vehicle alone to act as a satellite study, solely for blood chemistry and proof of absorption investigations. The last of these animals was sacrificed after the completion of 52 weeks of treatment. This study was conducted between 1989 to 1991 and was reported in report number 91/CID037/0644. Necropsy was completed on December 19, 1990 for males receiving 0.3% CD 271 aqueous gel, January 9, 1991 for females receiving 0.3% CD 271 aqueous gel and February 4, 1991 for all other animals.

The animals were inspected at least twice daily for evidence of reaction to treatment or ill-health. A more detailed weekly examination, which included palpation, was performed on each animal. Food consumptions were recorded for each week throughout the treatment period. Body weights were recorded weekly for the first 14 weeks of treatment, once fortnightly thereafter and before necropsy. All animals killed and any found dead were subjected to a detailed necropsy. Microscopic examination was performed on selected tissues from all mice of vehicle control (group 2) and high dose groups and from all mice of low and medium dose groups killed or dying during the treatment period. Selected tissues were examined for all female untreated control group (group 1). Tissue reported at macroscopic examination as being abnormal were examined for all mice except untreated control group (group 1).

III. b. Sponsor's Analyses

The sponsor indicated that all statistical analyses were performed against the vehicle control group (group 2). Similar to the rats study, the Cox's proportional hazards model and Tarone's partition of the Chi-square statistic were applied to the mortality data. Adjusted mortality rates have been estimated using Kaplan-Meier or Product Limit estimations. These rates are adjusted to account for animals which were censored and therefore whose week of death is unknown. Two analyses were performed. The first analysis takes humane kills as censored observations, while the second treats them as uncensored. The following table showed the numbers of animals killed on humane grounds due to severe dorsal abrasions.

	Males					Females				
Groups	1	2	3	4	5	1	2	3	4	5
Level (% w/w)	0	0	0.03	0.1	0.3	0	0	0.03	0.1	0.3
# of animals	2	1	5	5	20	2	0	1	6	6

The results showed that when the humane kills were treated as uncensored observations, Cox's test was statistically significant for males. This indicated the presence of differential mortality. In males, Tarone's test indicated the presence of a positive trend of mortality with dosage, also pairwise comparisons between the control group and intermediate and high dosage groups were statistically

significant. However, analysis treating the animals killed on humane grounds as censored observations, indicating no significant differences between the groups. The difference between the two analyses was, therefore, clearly a consequence of the inter-group variations in the number of animals killed on humane grounds. For females, a similar positive trend was observed. The pairwise comparison between the high dosage group and control group was statistically significant. Tables 21-24 and Figures 5-8 listed the above results.

Fisher's Exact probability test was applied to the tumor data analysis. The results showed that the incidences of vascular endothelial tumors (hemangioma or hemangiosarcoma) regardless of their primary tissue are significantly ($p < 0.05$) higher among high dose females than the vehicle control females. The sponsor compared the tumor incidences of this study with those of another 104 weeks CD-1 mouse study with two control groups (see Table 25). The results showed that the incidences of vascular endothelial tumors in high dose females (14%) was similar to those seen in the controls in the previous study (10% to 13%).

For the non-neoplastic findings, there is a statistically significant changes in the skin and spleen in high dose animals (see Tables 26 and 27). However, the observed skin irritancy was not associated with any neoplastic change. The sponsor indicated that the single papilloma at the application site on a medium dose female could not confidently be ascribed to treatment with CD 271 aqueous gel.

Based on the above test results, the sponsor concluded that "the topical application of CD 271 aqueous gel to CD-1 mice for their life-span did not demonstrate any oncogenic potential."

III.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas et al. (1977) were used to test for heterogeneity in survival distributions of two controls, low, medium, and high dose groups. The p-values of the Cox test were 0.0064 and 0.1764 for males and females, respectively. Hence, there was no statistically significant difference (at 0.05 level) in the survival distribution in female mice. However, there was a statistically significant difference (at 0.05 level) in the survival distribution in male mice. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.0013 and 0.1482 for males and females, respectively. The negative control group survival was compared with the vehicle control group survival. The test results showed that there was no significant difference in survival between two control groups in both sexes.

The intercurrent mortality rates for both male and female mice (see Table 28) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980). The time

intervals used 0-50, 51-80, and 81-104 weeks for controls, low, and medium dose groups; 0-50, 51-80, 81-98 weeks for male high dose groups; and 0-50, 51-80, 81-101 weeks for female high dose groups. Since there were two control groups in this study, three separate sets of analyses were applied to these data sets. In the first set of analyses (called C1), the data of negative control, low, medium, and high dose groups were used. In the second set of analyses (called C2), the data of vehicle control, low, medium, and high dose groups were used. In the third set of analyses (called C1+C2), the data of both controls, low, medium, and high dose groups were used. The actual dose levels 0, 0, 0.6, 2, and 6 mg/kg/administration were the scores assigned to the controls, low, medium, and high dose groups, respectively. The results of the analyses showed that there were significant (at 0.05 level) linear trends in the intercurrent mortality rate in both female (C1: p = 0.0299, C2: p = 0.0285, C1+C2: p = 0.0173) and male mice (C1: P = 0.0027, C2: P = 0.0038, C1+C2: P = 0.0005).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. Similar to the analyses of mortality data, three sets (C1, C2, and C1+C2) of analyses were performed on the tumor data. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in the spleen hemangiosarcoma and hemangioma in female mice (C1: P = 0.0962, **C2: P = 0.0372, C1+C2: P = 0.0405**). The incidence rates of this tumor are given in Table 29.

As mentioned previously, not all tissues of all animals were examined microscopically. Appendix II listed the tumor incidences and number of animals evaluated for each tumor type.

The reviewer also applied age-unadjusted (data constraint) exact permutation trend test to the incidence data of vascular endothelial tumors (hemangioma or hemangiosarcoma) regardless of their primary tissue in female mice. The results showed that there was a significant (at 0.05 level) positive linear trend in the vascular endothelial tumors (hemangioma or hemangiosarcoma) regardless of their primary tissue in female mice (C1: P = 0.2072, **C2: P = 0.0242**, C1+C2: P = 0.0663). However, the prevalence rate of vascular endothelial tumors (hemangioma or hemangiosarcoma) in the concurrent control group in female mice is greater than one percent. They are considered as common tumors in this strain of mice. For a common tumor, we consider a positive linear trend not to occur by chance of variation only if the p-value is smaller than 0.01. Therefore, we do not regard the positive linear trend in vascular endothelial tumors (hemangioma or hemangiosarcoma) in female mice as statistically significant. The incidence rates of this tumor are given in Table 25.

IV. Summary

IV. a. The Rat Study - 104 weeks Oncogenicity Phase

The oncogenic potential of adapalene topical solution was evaluated in this rat study. The test material was administered via the diet continuously to the groups of 60 male and 60 female CD rats at dosage levels of 0.15, 0.5 or 1.5 mg/kg/day for 104 weeks. A similarly constituted control group received untreated diet.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no statistically significant difference (at 0.05 level) in the survival distribution in both sexes.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in either female ($p = 0.3667$) or male rats ($p = 0.4869$). Noted that the data in sponsor's submitted diskettes include humane kills animals treated as uncensored observations.

Results of tumor data analyses showed that there was a significant (at 0.05 level) positive linear trend in thyroids follicular cell adenoma and carcinoma combined ($p = 0.0049$) in female rats and in adrenal benign and malignant pheochromocytomas ($p = 0.0051$) in male rats. There were marginally significant positive linear trends in H'poietic histiocytic sarcoma ($p = 0.0696$) and in H'poietic monocytic leukaemia ($p = 0.0696$) in male rats.

As mentioned previously, not all tissues of all animals were examined microscopically. Due to the constraint of the format of data sent by the sponsor, the above analyses are assumed that all of animals are examined for selected tumor/organ types. For example, there are 60, 59, 60, and 60 female rats were examined microscopically for thyroids in control, low, medium, and high dose groups. However, the reviewer assumed that there are 60 females for each group were examined microscopically for thyroids.

IV. b. The Rat Study - 78 weeks Toxicity Phase

In the 78-week chronic toxicity phase, groups of 20 male and 20 female CD rats received CD 271 continuously via the diet at doses of 0.15, 0.5 or 1.5 mg/kg/day. A similarly constituted control group received untreated diet. An additional ten male and ten female rats were assigned to each group in a satellite study, solely for proof of absorption and blood chemistry investigations.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no statistically significant difference (at 0.05

level) in the survival distribution in both sexes.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in either female ($p = 0.1914$) or male rats ($p = 0.2055$).

Results of tumor data analyses showed that there was a significant (at 0.05 level) positive linear trend in adrenal benign and malignant pheochromocytomas ($p = 0.0003$) in male rats. Noted that there are only 20 animals per sex/group in this study.

IV.c. The Rat Study - Combined 104 weeks Oncogenicity and 78 weeks Toxicity Phases

The reviewer also evaluated the combined survival and tumor data of oncogenicity and toxicity studies.

The intercurrent mortality rates for both male and female rats were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980). The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in either female ($p = 0.3151$) or male rats ($p = 0.497$).

Tumor data analyses showed that there were significant (at 0.05 level) positive linear trends in thyroids follicular cell adenoma and carcinoma ($p = .0017$) in female rats and in adrenal benign and malignant pheochromocytomas ($p < 0.0001$) in male rats. There were marginally significant positive linear trends in H'poietic histiocytic sarcoma ($p = 0.0605$) and in H'poietic monocytic leukaemia ($p = 0.0853$) in male rats.

IV. d. The Mouse study

In this study, groups of 50 male and 50 female CD-1 mice received CD 271 aqueous gel suspension, by topical application to the clipped dorsum, at dose levels of 0, 0.03, 0.1, and 0.3% w/w at a volume dosage of 2 mL/kg bodyweight corresponding to 0, 0.6, 2.0, and 6.0 mg/kg/administration respectively. A similarly constituted reference group received the vehicle gel alone at the same frequency as the treated groups. A further similarly constituted group received no treatment and was clipped only. For the first 19 weeks of treatment, the aqueous gel formulations were applied seven times a week. However, on account of the severity of signs observed at the application site of animals treated with CD 271 aqueous gel, the frequency of application was reduced to five times a week. For similar reasons the frequency of application was further reduced to

three occasions each week from week 63. For males and females of the high dosage group treatment continued for 98 and 101 weeks respectively. The remaining groups were treated for 104 weeks.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no statistically significant difference (at 0.05 level) in the survival distribution in female mice. However, there was a statistically significant difference (at 0.05 level) in the survival distribution in male mice. The negative control group survival was compared with the vehicle control group survival. The test results showed that there was no significant difference in survival between two control groups in both sexes.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Since there were two control groups in this study, three separate sets of analyses were applied to these data sets. In the first set of analyses (called C1), the data of negative control, low, medium, and high dose groups were used. In the second set of analyses (called C2), the data of vehicle control, low, medium, and high dose groups were used. In the third set of analyses (called C1+C2), the data of both controls, low, medium, and high dose groups were used. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there were significant (at 0.05 level) linear trends in the intercurrent mortality rate in both female (C1: p = 0.0299, C2: p = 0.0285, C1+C2: p = 0.0173) and male mice (C1: P = 0.0027, C2: P = 0.0038, C1+C2: P = 0.0005).

Results of the tumor data analyses showed that there was a significant (at 0.05 level) <u>positive</u> linear trend in the spleen hemangiosarcoma and hemangioma in female mice (C1: P = 0.0962, **C2: P = 0.0372, C1+C2: P = 0.0405**). The reviewer also applied <u>age-unadjusted</u> (data constraint) exact permutation trend test to the incidence data of vascular endothelial tumors (hemangioma or hemangiosarcoma) regardless of their primary tissue in female mice. The incidences are 6/50, 1/50, 3/50, 6/50, and 7/50 for negative control, vehicle control, low, medium, and high dose groups. The results showed that there was a significant (at 0.05 level) <u>positive</u> linear trend in the vascular endothelial tumors (hemangioma or hemangiosarcoma) regardless of their primary tissue in female mice (C1: P = 0.2072, **C2: P = 0.0242**, C1+C2: P = 0.0663). However, the prevalence rate of vascular endothelial tumors (hemangioma or hemangiosarcoma) in the concurrent control group in female mice is greater than one percent. They are considered as common tumors in this strain of mice. For a common tumor, we consider a positive linear trend not to occur by chance of variation only if the p-value is smaller than 0.01. Therefore, we do not regard the positive linear trend in vascular endothelial tumors (hemangioma or hemangiosarcoma) in female mice as statistically significant.

Daphne Lin

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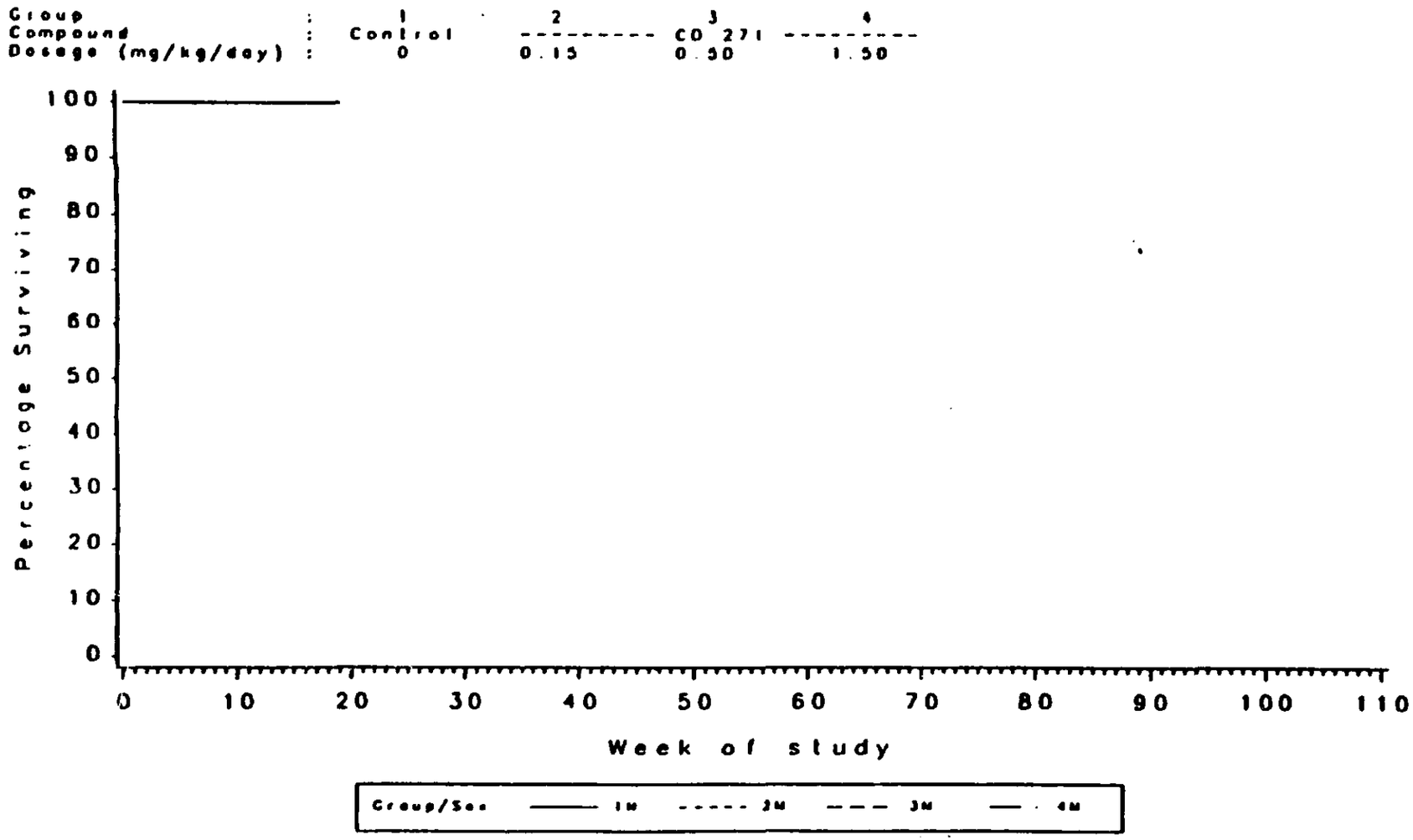
HFD-502/Dr. Taylor
HFD-715/DRU 2.1.1, Adapalene, Owen/Galderma Lab.

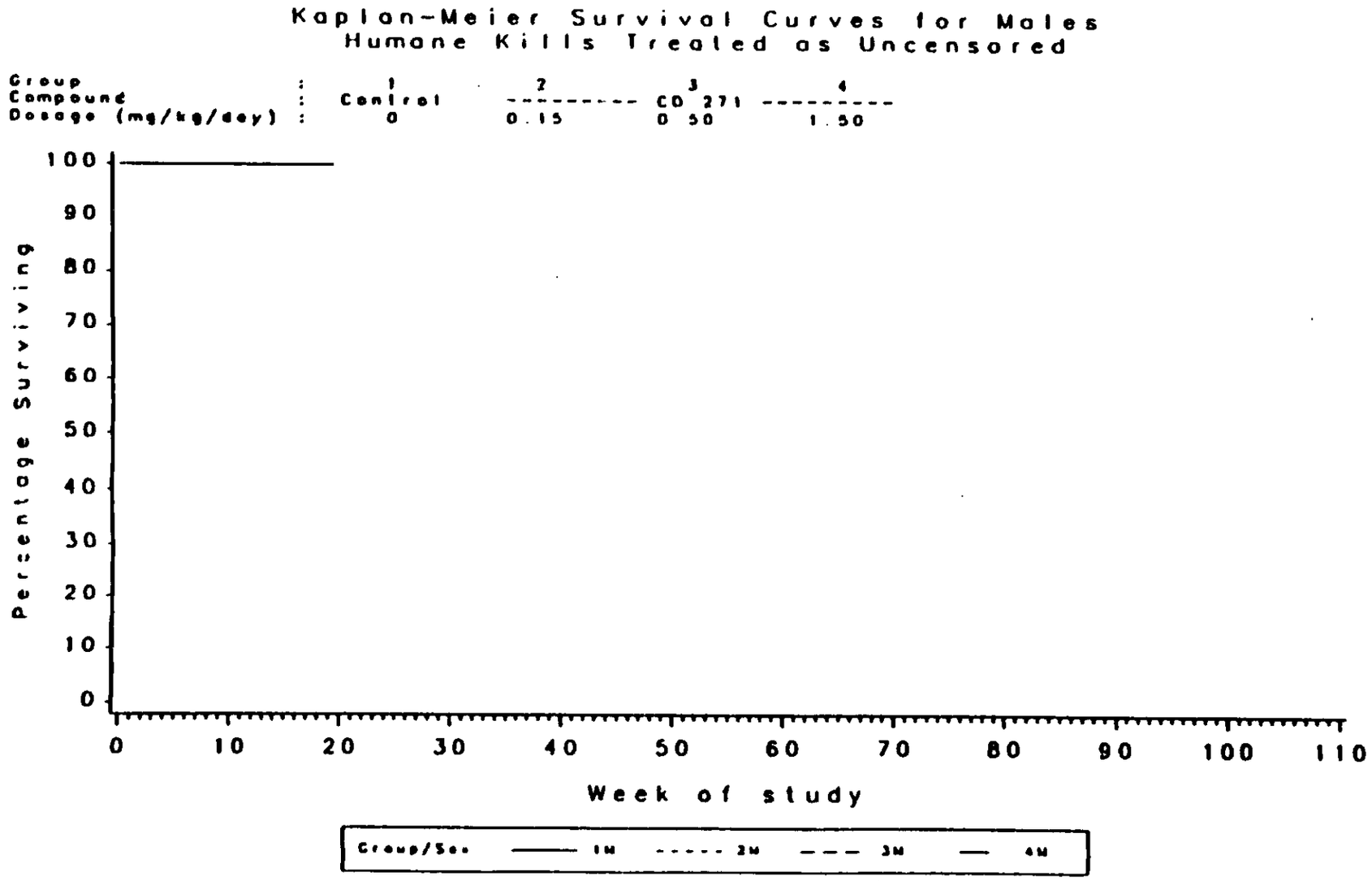
Figure 1

Kaplan-Meier Survival Curves for Males
Humane Kills Treated as Censored



CID053

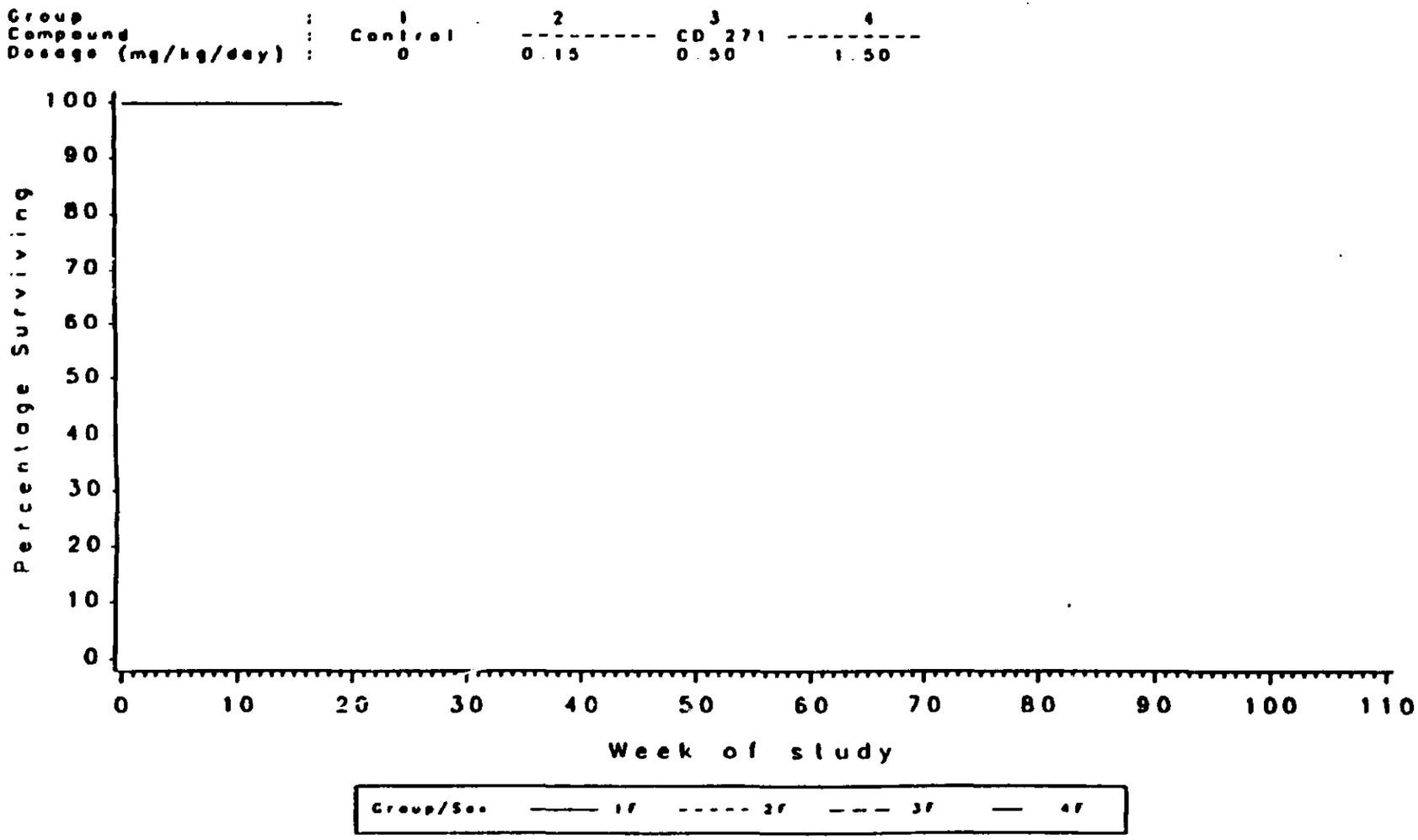
Figure 2



CID053

Figure 3

Kaplan-Meier Survival Curves for Females
Humane Kills Treated as Censored



CID053

Figure 4

Kaplan-Meier Survival Curves for Females
Humane Kills Treated as Uncensored

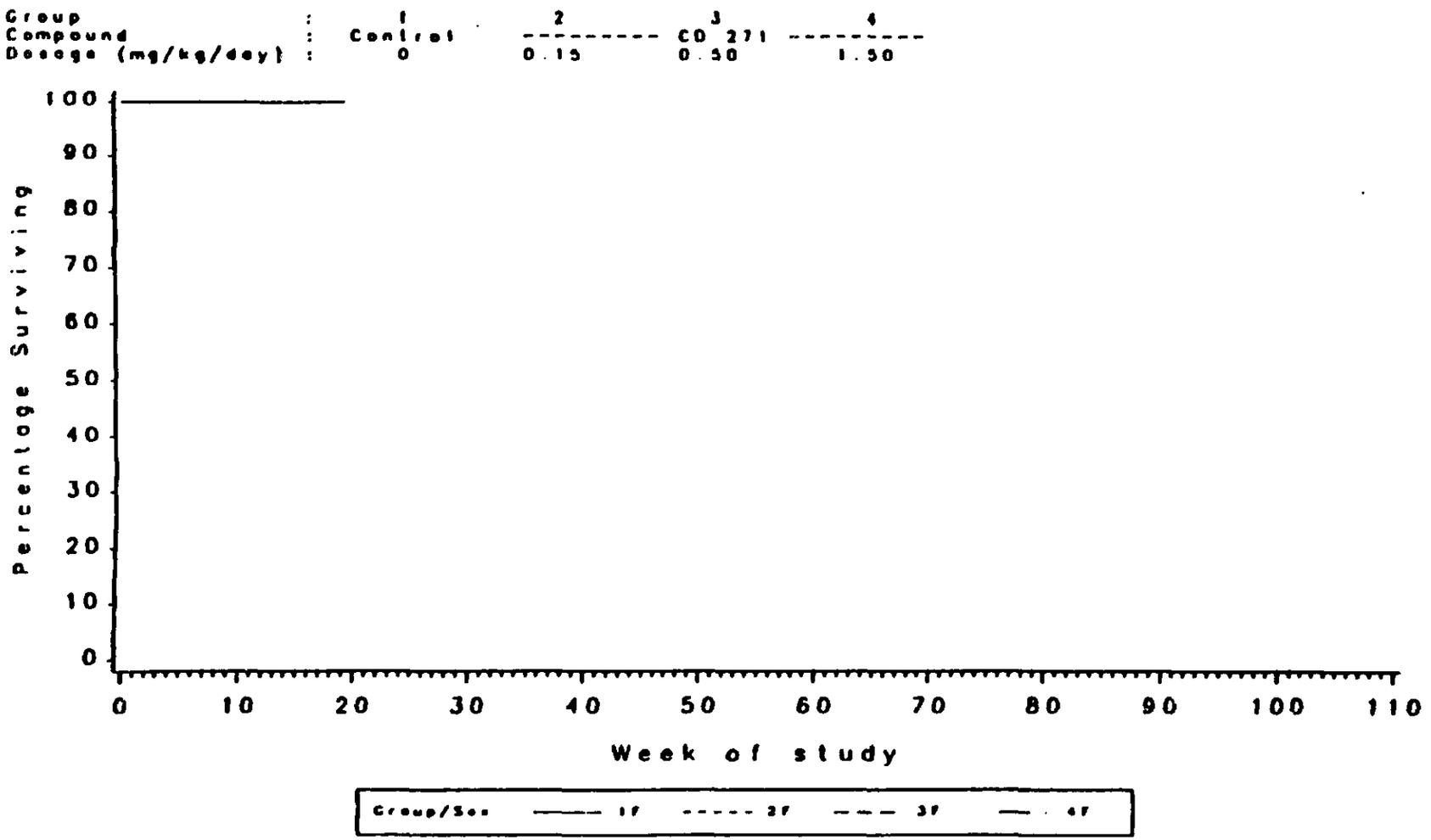


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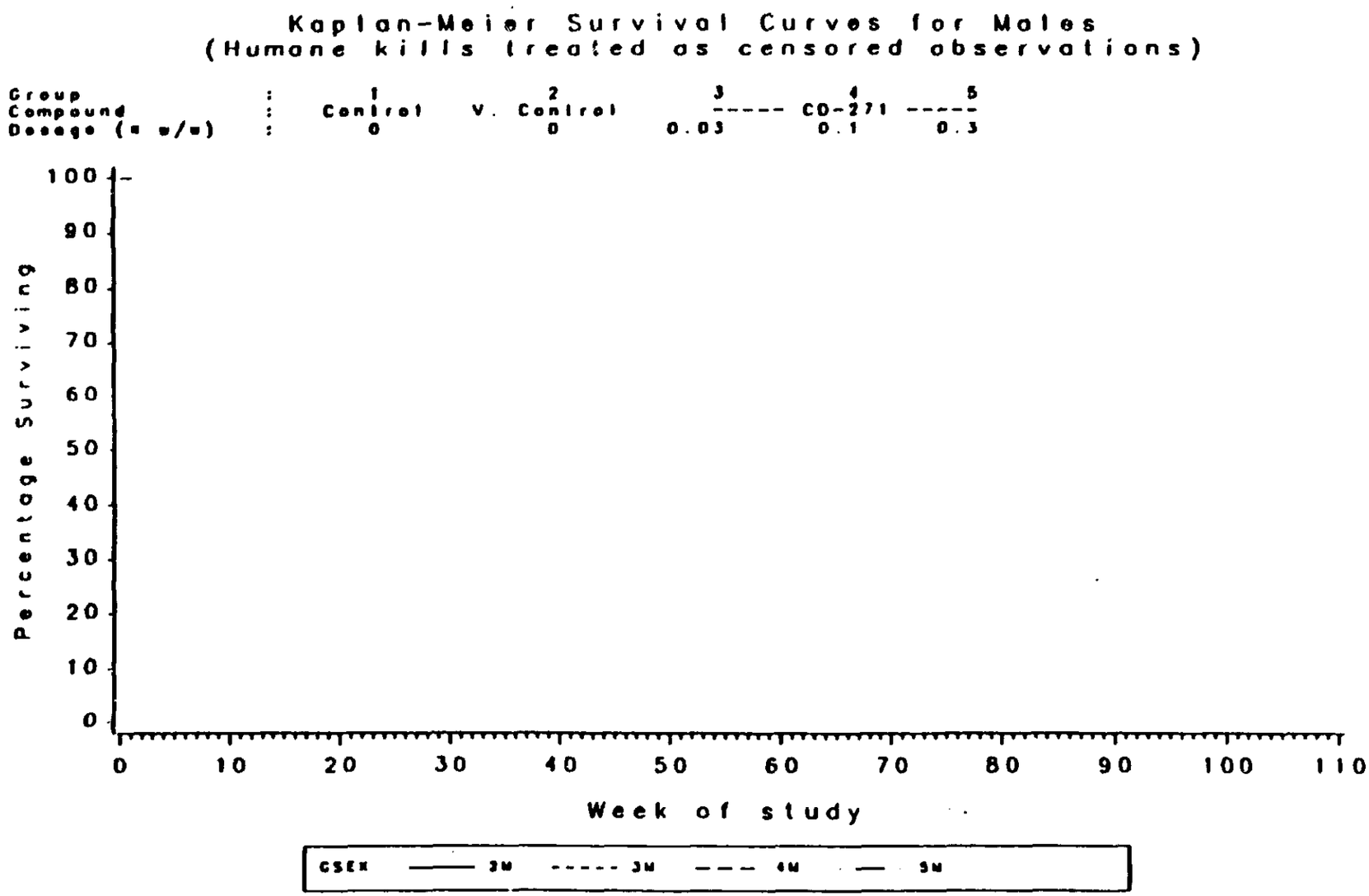
Figure 5



C1D037

Figure 6

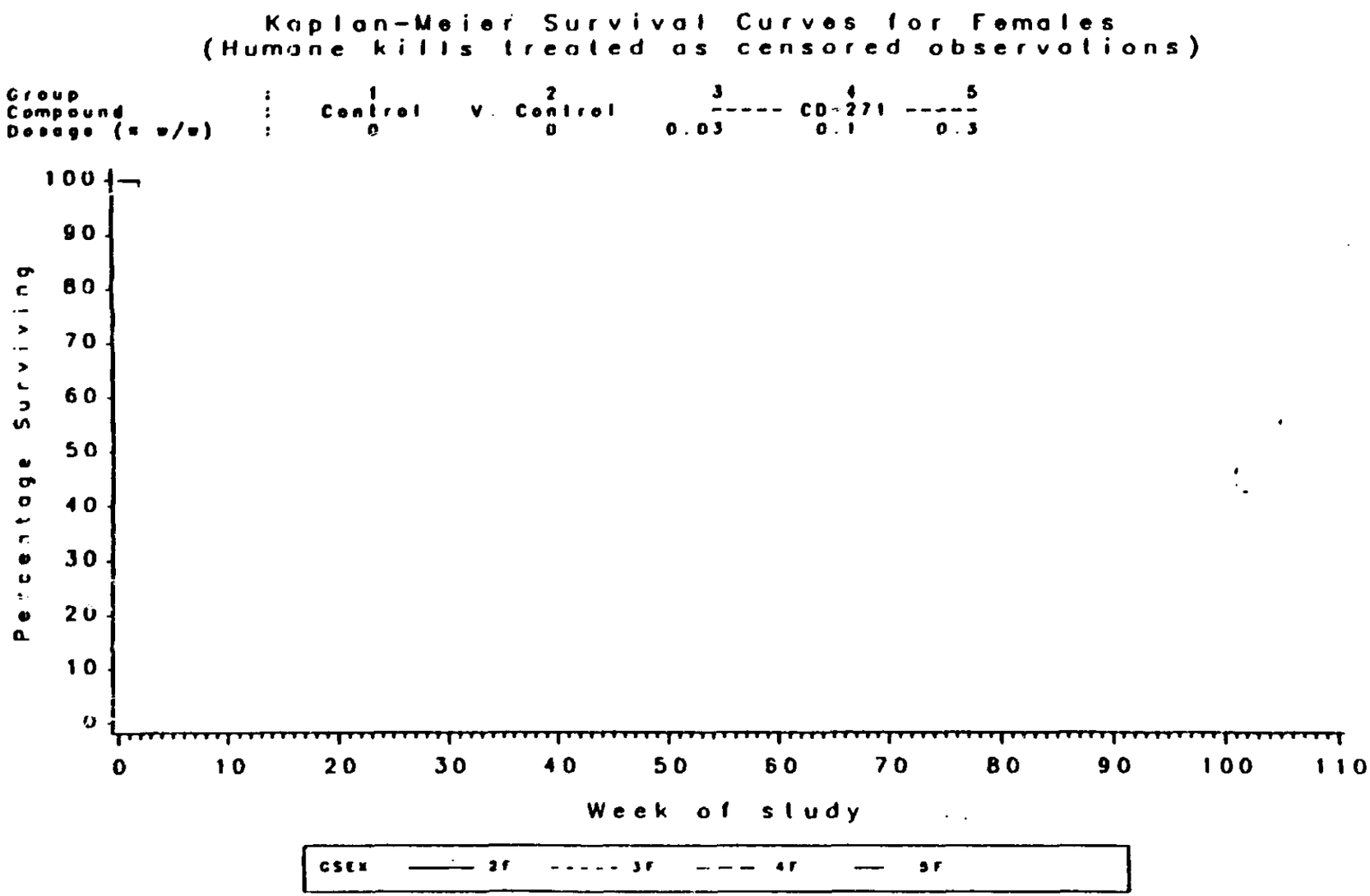


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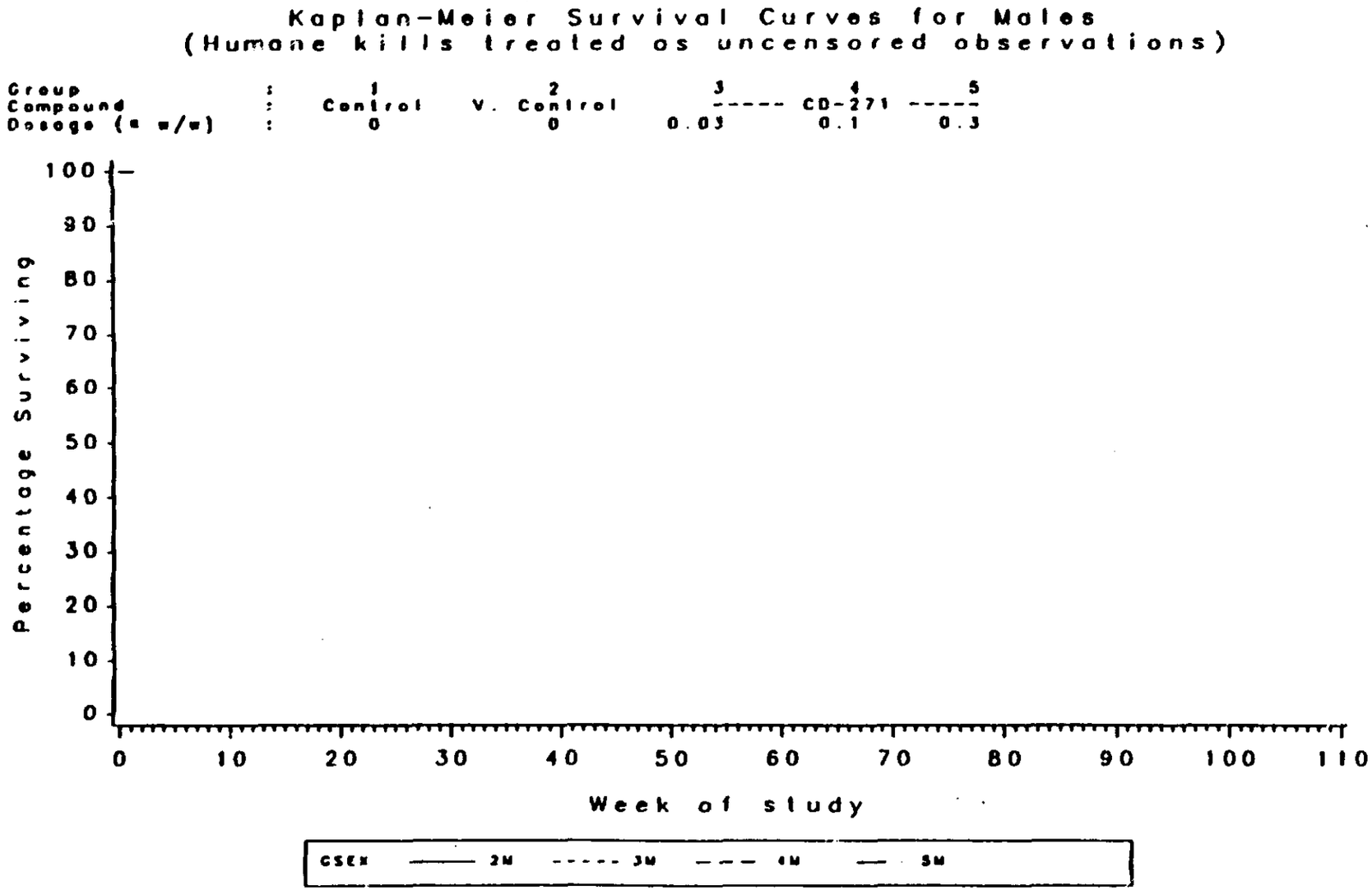
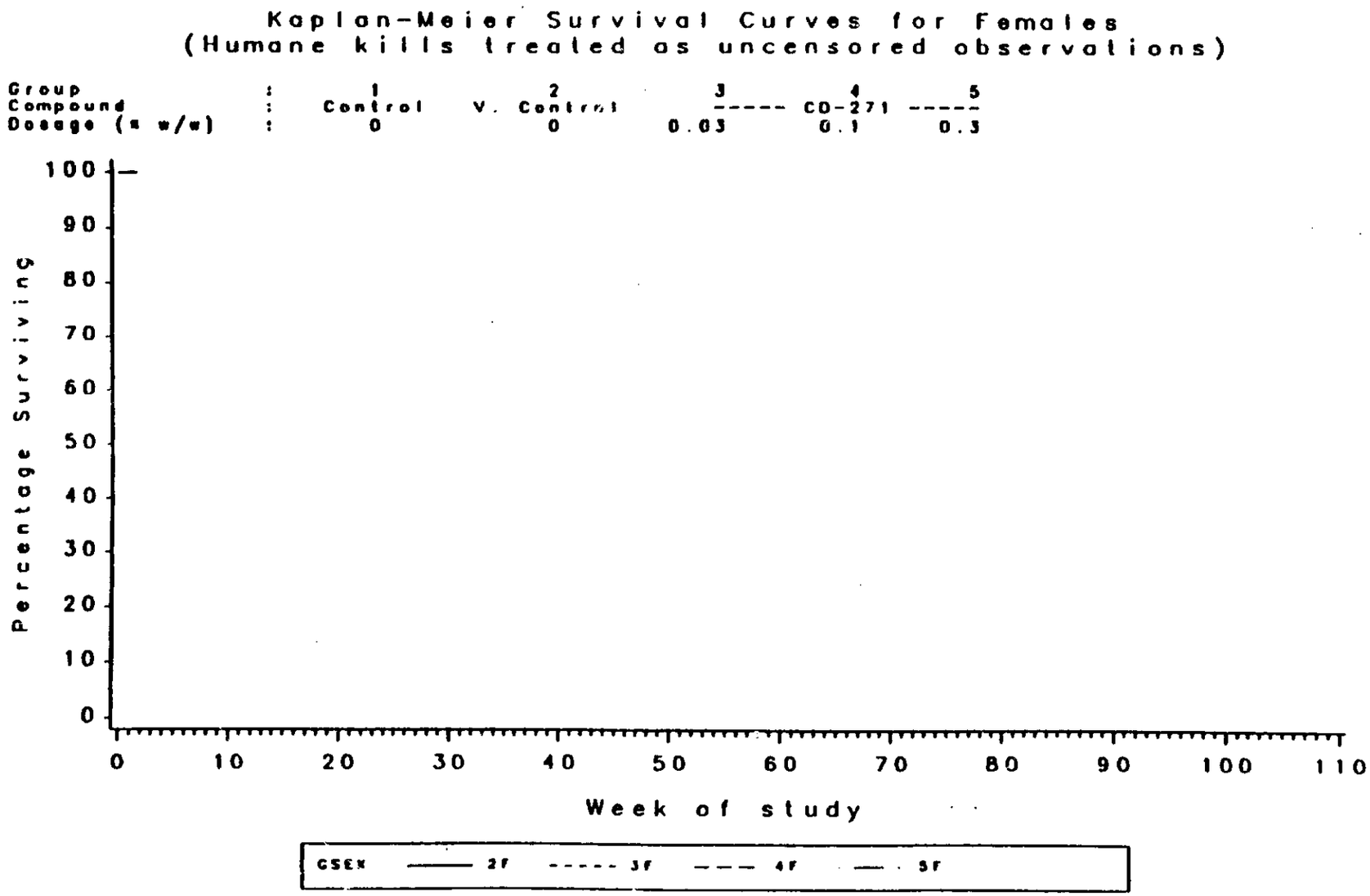
Figure



CID037

Figure 8



CID037

Table 1

Statistical analysis of differential mortality in males
Humane kills treated as censored

Dosage (mg/kg/day)	Control	0.15	0.50	1.50
Crude Rates[1]	37/60 (62%)	40/60 (67%)	43/60 (72%)	38/60 (63%)
Adjusted Rates[2]	67.7%	69.9%	79.0%	70.0%
Cox's Test[3]	p=0.240	p=0.895	p=0.160	p=0.919
Tarone's Test:[4]				
two-tailed test	p=0.858			
one-tailed test (+ve)	p=0.443			
Departure from Trend	p=0.123			

Notes:

1) Crude mortality rates defined as the number of animals dying (Found Dead and Killed *In Extremis*) during the study, over the total number of animals per group.
2) Kaplan-Meier estimated mortality rates at the end of study after adjusting for censored animals (Humane kills, accidental deaths etc.)
3) Beneath the control incidence is the p-value for Cox's test for homogeneity of survival curves. Beneath each treated group's incidence is the p-value corresponding to the Cox test pairwise comparisons between the treated and control groups.
4) Three p-values are tabulated for Tarone's test. The first value is that for a two-tailed test of trend. The second figure is for a one-tailed test of positive trend. The third value is the p-value for the test of departure from a linear trend.

Table 2

Statistical analysis of differential mortality in females
Humane kills treated as censored

Dosage (mg/kg/day)	Control	0.15	0.50	1.50
Crude Rates[1]	19/60 (32%)	24/60 (40%)	21/60 (35%)	19/60 (32%)
Adjusted Rates[2]	47.0%	53.1%	47.3%	43.9%
Cox's Test[3]	p=0.779	p=0.989	p=0.799	p=0.665
Tarone's Test:[4]				
two-tailed test	p=0.385			
one-tailed test (-ve)	p=0.207			
Departure from Trend	p=0.843			

Notes:

1) Crude mortality rates defined as the number of animals dying (Found Dead and Killed *In Extremis*) during the study, over the total number of animals per group.
2) Kaplan-Meier estimated mortality rates at the end of study after adjusting for censored animals (Humane kills, accidental deaths etc.)
3) Beneath the control incidence is the p-value for Cox's test for homogeneity of survival curves. Beneath each treated group's incidence is the p-value corresponding to the Cox test pairwise comparisons between the treated and control groups.
4) Three p-values are tabulated for Tarone's test. The first value is that for a two-tailed test of trend. The second figure is for a one-tailed test of positive trend. The third value is the p-value for the test of departure from a linear trend.

Table 3

Statistical analysis of differential mortality in males
Humane kills treated as uncensored

Dosage (mg/kg/day)	Control	0.15	0.50	1.50
Crude Rates[1]	45/60 (75%)	45/60 (75%)	51/60 (85%)	45/60 (75%)
Adjusted Rates[2]	75.0%	75.0%	85.0%	75.1%
Cox's Test[3]	p=0.159	p=0.999	p=0.145	p=0.817
Tarone's Test:[4]				
two-tailed test	p=0.871			
one-tailed test (+ve)	p=0.448			
Departure from Trend	p=0.075			

Notes:

1) Crude mortality rates defined as the number of animals dying (Found Dead and Killed *In Extremis*) during the study, over the total number of animals per group.
2) Kaplan-Meier estimated mortality rates at the end of study after adjusting for censored animals (accidental deaths etc.)
3) Beneath the control incidence is the p-value for Cox's test for homogeneity of survival curves. Beneath each treated group's incidence is the p-value corresponding to the Cox test pairwise comparisons between the treated and control groups.
4) Three p-values are tabulated for Tarone's test. The first value is that for a two-tailed test of trend. The second figure is for a one-tailed test of positive trend. The third value is the p-value for the test of departure from a linear trend.

Table 4

Statistical analysis of differential mortality in females
Humane kills treated as uncensored

Dosage (mg/kg/day)	Control	0.15	0.50	1.50
Crude Rates[1]	49/60 (82%)	49/60 (82%)	44/60 (73%)	46/60 (77%)
Adjusted Rates[2]	81.7%	81.7%	73.3%	77.1%
Cox's Test[3]	p=0.406	p=0.555	p=0.162	p=0.318
Tarone's Test:[4]				
two-tailed test	p=0.137			
one-tailed test (-ve)	p=0.073			
Departure from Trend	p=0.704			

Notes:

1) Crude mortality rates defined as the number of animals dying (Found Dead and Killed *In Extremis*) during the study, over the total number of animals per group.
2) Kaplan-Meier estimated mortality rates at the end of study after adjusting for censored animals (accidental deaths etc.)
3) Beneath the control incidence is the p-value for Cox's test for homogeneity of survival curves. Beneath each treated group's incidence is the p-value corresponding to the Cox test pairwise comparisons between the treated and control groups.
4) Three p-values are tabulated for Tarone's test. The first value is that for a two-tailed test of trend. The second figure is for a one-tailed test of positive trend. The third value is the p-value for the test of departure from a linear trend.

Table 5

Incidences (%) of phaeochromocytoma among male CD rats from 104-week oncogenicity studies conducted at 1986 and 1987

Study reference numbers	Benign phaeochromocytoma	Malignant phaeochromocytoma	Number examined
CDR043[1]	4(8)	0(0)	50
CDR043[2]	6(12)	0(0)	50
CDR044	11(22)	0(0)	49
CDR060	4(8)	2(4)	50
CDR061[1]	12(24)	3(6)	50
CDR061[2]	12(24)	3(6)	50
This study: Group			
1	7(12)	2(3)	60
2	9(15)	3(5)	60
3	10(17)	0(0)	60
4	18[a](30)	3(5)	60

* Historical control studies were selected to ensure that the conditions of animal husbandry were similar to those used for this study.

[1] and [2] are used to identify control groups for studies with two such groups.

a Significantly different from controls, $P < 0.05$

Table 6

Incidences (%) of tumours of pancreatic islet cells among male CD rats from 104-week oncogenicity studies conducted at 1986 and 1987.

Study reference numbers	Islet cell adenoma	Islet cell carcinoma	Islet cell tumour	Number examined
CDR043[1]	5(10)	0(0)	5(10)	50
CDR043[2]	2(4)	0(0)	2(4)	50
CDR044	5(10)	1(2)	6(12)	50
CDR060	4(8)	1(2)	5(10)	50
CDR061[1]	3(6)	3(6)	6(12)	50
CDR061[2]	8(16)	2(4)	10(20)	50
This study: Group				
1	2(3)	1(2)	3(5)	60
2	4(7)	4(7)	8(14)	59
3	2(3)	4(7)	6(10)	60
4	5(8)	4(7)	9(15)	59

* Historical control studies were selected to ensure that the conditions of animal husbandry were similar to those used for this study

[1] and [2] are used to identify control groups for studies with two such groups

Table 7

Incidence (%) of follicular cell tumours of the thyroid among female CD rats from 104-week oncogenicity studies conducted at 1986 and 1987

Study reference numbers	Follicular cell adenoma	Follicular cell carcinoma	Follicular cell tumour	Number examined
CDR043'	0(0)	0(0)	0(0)	50
CDR043"	2(4)	0(0)	2(4)	50
CDR044	1(2)	0(0)	1(2)	50
CDR060	2(4)	2(4)	4(8)	49
CDR061'	2(4)	5(10)	6(12)	50
CDR061"	1(2)	1(2)	2(4)	50
This study group				
1	0(0)	0(0)	0(0)	60
2	1(2)	0(0)	1(2)	59
3	0(0)	1(2)	1(2)	60
4	4(7)	1(2)	5[a](8)	60

* Historical control studies were selected to ensure that the conditions of animal husbandry were similar to those used for this study

' and " are used to identify control groups for studies with two such groups

a Significantly different from controls, $P < 0.05$

Table 8

TABLE 1

Cumulative mortality

Group	:	1	2	3	4
Compound	:	Control	----- CD 271 -----		
Dosage (mg/kg/day)	:	0	0.15	0.5	1.5

Week number	Group and sex							
	1M	2M	3M	4M	1F	2F	3F	4F
0-33	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0
35	0	0	0	1	0	0	0	0
36	0	0	0	1	1	0	0	0
37-38	0	0	0	1	1	0	0	0
39	0	0	0	1	1	0	0	1
40-41	0	0	0	1	1	0	0	1
42	0	0	1	1	1	0	0	1
43-47	0	0	1	1	1	0	0	1
48	0	0	1	1	1	1	0	1
49-50	0	0	1	1	1	1	0	1
51	0	1	1	1	1	1	0	1
52	0	2	1	2	1	1	0	1
53-55	0	2	1	2	1	1	0	1
56	0	3	1	2	1	1	0	1
57	1	4	1	2	1	2	0	1
58	1	4	2	2	1	2	0	1
59	1	4	2	2	2	2	0	1
60	1	4	2	2	2	2	0	1

TABLE I - continued

Cumulative mortality

Group	:	1	2	3	4
Compound	:	Control	----- CD 271 -----		
Dosage (mg/kg/day)	:	0	0.15	0.5	1.5

Week number	Group and sex 1M	2M	3M	4M	1F	2F	3F	4F
61	1	4	2	2	2	2	1	1
62	1	4	2	2	2	2	1	2
63	1	4	2	2	2	2	1	2
64	2	4	2	2	3	2	2	2
65	2	4	2	4	3	2	2	2
66	2	5	2	4	4	2	2	2
67	2	6	2	4	4	2	2	2
68	2	6	2	4	4	2	2	2
69	2	6	4	4	4	3	2	3
70	2	6	4	4	4	3	3	3
71	2	6	4	5	5	3	4	3
72	2	6	4	5	5	3	4	3
73	2	6	4	5	5	4	4	3
74	3	6	4	5	5	4	4	3
75	3	7	4	6	5	4	4	3
76	3	8	4	7	5	4	4	3
77	3	9	4	8	6	4	4	3
78	4	9	6	8	6	4	4	3
79	4	9	6	8	6	4	4	3

Table 9
Oncogenicity Study
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	60	5	8.33	60	2	3.33	60	4	6.66	60	1	1.66
51-80	55	11	20	58	16	27.6	56	22	39.3	59	13	22
81-104	44	29	65.9	42	27	64.3	34	25	73.5	46	34	73.9
Term.	15			15			9			12		

Female Rats

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	60	2	3.33	60	2	3.33	60	1	1.66	60	2	3.33
51-80	58	22	37.9	58	12	20.7	59	14	23.7	58	16	27.6
81-104	36	25	69.4	46	35	76	45	29	64.4	42	30	71.4
Term.	11			11			16			12		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 10
Tumor Incidence Rates
Female Rats, Thyroids Follicular Cell Tumors

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	2	0	2	0	1	0	2
51-80	0	22	0	12	0	14	0	16
81-104	0	25	0	35	1	29	4	30
terminal	0	11	1	11	0	16	1	12
Total	0	60	1	60	1	60	5	60

p-value = 0.0049

Table 11
Tumor Incidence Rates
Male Rats, Adrenal Benign and Malignant Pheochromocytomas

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	5	0	2	0	4	0	1
51-80	1	11	2	16	2	22	3	13
81-104	7	29	4	27	6	25	13	34
terminal	1	15	6	15	2	9	5	12
Total	9	60	12	60	10	60	21	60

p-value = 0.0051

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 12
Tumor Incidence Rates
Male Rats, H'poietic Monocytic Leukaemia

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	1	5	0	2	0	4	1	1
51-80	0	11	0	16	1	22	0	13
81-104	0	29	2	27	1	25	3	34
terminal	0	15	0	15	0	9	0	12
Total	1	60	2	60	2	60	4	60

p-value = 0.0696

Table 13
Tumor Incidence Rates
Male Rats, H'poietic Histiocytic Sarcoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	5	0	2	0	4	0	1
51-80	0	11	0	16	0	22	0	13
81-104	0	29	0	27	0	25	1	34
terminal	0	15	0	15	0	9	1	12
Total	0	60	0	60	0	60	2	60

p-value = 0.0696

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 14
Toxicity Study
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	20	0	0	20	0	0	20	1	5	20	1	5
51-78	20	4	25	20	9	45	19	5	26.3	19	7	36.8
Term.	16			11			14			12		

Female Rats

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	20	1	5	20	1	5	20	0	0	20	1	5
51-78	19	5	26.3	19	3	15.7	20	4	20	19	2	10.5
Term.	14			16			16			17		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 15
Tumor Incidence Rates
Male Rats, Adrenal Benign and Malignant Pheochromocytomas

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	0	0	0	0	1	0	1
51-78	0	4	0	9	1	5	1	7
terminal	2	16	0	11	2	14	7	12
Total	2	20	0	20	3	20	8	20

p-value = 0.0003

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 16
Oncogenicity and Toxicity Studies
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	80	5	6.25	80	2	2.5	80	5	6.25	80	2	2.5
51-78	75	14	18.6	78	21	26.9	75	23	30.6	78	18	23.0
79-79	61	16	26.2	57	11	19.3	52	14	26.9	60	12	20
80-104	45	30	6.66	46	31	67.4	38	29	76.3	48	36	75
Term.	15			15			9			12		

Female Rats

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	80	3	3.75	80	3	3.75	80	1	1.25	80	3	3.75
51-78	77	25	32.4	77	12	15.6	79	16	20.2	77	15	19.4
79-79	52	14	26.9	65	16	24.6	63	16	25.4	62	17	27.4
80-104	38	27	71.0	49	38	77.5	47	31	65.9	45	33	73.3
Term.	11			11			16			12		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 17
Tumor Incidence Rates
Female Rats, Thyroids Follicular Cell Tumors

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	3	0	3	0	1	0	3
51-78	0	25	0	12	0	16	0	15
79-79	0	14	0	16	0	16	1	17
80-104	0	27	0	38	1	31	4	33
terminal	0	11	1	11	0	16	1	12
Total	0	80	1	80	1	80	6	80

p-value = 0.0017

Table 18
Tumor Incidence Rates
Male Rats, Adrenal Benign and Malignant Pheochromocytomas

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	5	0	2	0	5	0	2
51-78	1	14	1	21	3	23	2	18
79-79	2	16	0	11	2	14	7	12
80-104	7	30	5	31	6	29	15	36
terminal	1	15	6	15	2	9	5	12
Total	11	80	12	80	13	80	29	80

p-value < 0.0001

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 19
Tumor Incidence Rates
Male Rats, H'poietic Histiccytic Sarcoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	5	0	2	0	5	0	2
51-78	1	14	0	21	1	23	0	18
79-79	0	16	0	11	0	14	1	12
80-104	0	30	0	31	0	29	1	36
terminal	0	15	0	15	0	9	1	12
Total	1	80	0	80	1	80	3	80

p-value = 0.0605

Table 20
Tumor Incidence Rates
Male Rats, H'poietic Monocytic Leukaemia

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	1	5	0	2	1	5	1	2
51-78	0	14	0	21	1	23	0	18
79-79	0	16	0	11	0	14	0	12
80-104	0	30	2	31	1	29	3	36
terminal	0	15	0	15	0	9	0	12
Total	1	80	2	80	3	80	4	80

p-value = 0.0853

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 21

Statistical analysis of differential mortality in males (treating humane kills as censored)

Dosage (% w/w)	V Control	0.03	0.1	0.3
Crude Rates[1]	17/50 (34%)	20/50 (40%)	25/50 (50%)	11/50 (22%)
Adjusted Rates[2]	37.1%	45.8%	61.0%	36.4%
Cox's Test[3]	p=0.309	p=0.516	p=0.104	p=0.934
Tarone's Test:[4]				
two-tailed test	p=0.443			
one-tailed test (-ve)	p=0.238			
Departure from Trend	p=0.222			

Notes:

1) Crude mortality rates defined as the number of animals dying (Found Dead and Killed *In Extremis*) during the study, over the total number of animals per group.
2) Kaplan-Meier estimated mortality rates at the end of study after adjusting for censored animals (Humane kills, accidental deaths etc.)
3) Beneath the control incidence is the p-value for Cox's test for homogeneity of survival curves. Beneath each treated group incidence is the p-value corresponding to the Cox test pairwise comparisons between the treated group and control group.
4) Three p-values are tabulated for Tarone's test. The first value is for a two-tailed test of trend. The second figure is for a one-tailed test for negative trend. The third value is the p-value for the test of departure from a linear trend.

Table 22

Statistical analysis of differential mortality in females (treating humane kills as censored)

Dosage (% w/w)	V Control	0.03	0.1	0.3
Crude Rates[1]	18/50 (36%)	21/50 (42%)	17/50 (34%)	24/50 (48%)
Adjusted Rates[2]	39.4%	45.9%	44.4%	57.7%
Cox's Test[3]	p=0.240	p=0.813	p=0.956	p=0.134
Tarone's Test:[4]				
two-tailed test	p=0.089			
one-tailed test (+ve)	p=0.050a			
Departure from Trend	p=0.231			

Notes:

a) Statistically significant at the 5% level ($p<0.05$)
1) Crude mortality rates defined as the number of animals dying (Found Dead and Killed *In Extremis*) during the study, over the total number of animals per group.
2) Kaplan-Meier estimated mortality rates at the end of study after adjusting for censored animals (Humane kills, accidental deaths etc.)
3) Beneath the control incidence is the p-value for Cox's test for homogeneity of survival curves. Beneath each treated group incidence is the p-value corresponding to the Cox test pairwise comparisons between the treated group and control group.
4) Three p-values are tabulated for Tarone's test. The first value is for a two-tailed test of trend. The second figure is for a one-tailed test for positive trend. The third value is the p-value for the test of departure from a linear trend.

Table 23

Statistical analysis of differential mortality in males (treating humane kills as uncensored)

Dosage (% w/w)	V Control	0.03	0.1	0.3
Crude Rates[1]	23/50 (46%)	27/50 (54%)	35/50 (70%)	33/50 (66%)
Adjusted Rates[2]	46.0%	55.1%	70.0%	67.3%
Cox's Test[3]	p=0.019a	p=0.432	p=0.047a	p=0.009b
Tarone's Test:[4]				
two-tailed test	p=0.002b			
one-tailed test (+ve)	p<0.001c			
Departure from Trend	p=0.945			

Notes:

a) Statistically significant at the 5% level ($p<0.05$)
b) Statistically significant at the 1% level ($p<0.01$)
c) Statistically significant at the .1% level ($p<0.001$)
1) Crude mortality rates defined as the number of animals dying (Found Dead and Killed *In Extremis*) during the study, over the total number of animals per group.
2) Kaplan-Meier estimated mortality rates at the end of study after adjusting for censored animals (Humane kills, accidental deaths etc.)
3) Beneath the control incidence is the p-value for Cox's test for homogeneity of survival curves. Beneath each treated group incidence is the p-value corresponding to the Cox test pairwise comparisons between the treated group and control group.
4) Three p-values are tabulated for Tarone's test. The first value is for a two-tailed test of trend. The second figure is for a one-tailed test for positive trend. The third value is the p-value for the test of departure from a linear trend.

Table 24

Statistical analysis of differential mortality in females (treating humane kills as uncensored)

Dosage (% w/w)	V Control	0.03	0.1	0.3
Crude Rates[1]	25/50 (50%)	28/50 (56%)	31/50 (62%)	35/50 (70%)
Adjusted Rates[2]	51.0%	56.6%	62.0%	70.0%
Cox's Test[3]	p=0.098	p=0.868	p=0.247	p=0.048a
Tarone's Test:[4]				
two-tailed test	p=0.015a			
one-tailed test (+ve)	p=0.008b			
Departure from Trend	p=0.819			

Notes:

a) Statistically significant at the 5% level ($p<0.05$)
b) Statistically significant at the 1% level ($p<0.01$)
1) Crude mortality rates defined as the number of animals dying (Found Dead and Killed *In Extremis*) during the study, over the total number of animals per group.
2) Kaplan-Meier estimated mortality rates at the end of study after adjusting for censored animals (Humane kills, accidental deaths etc.)
3) Beneath the control incidence is the p-value for Cox's test for homogeneity of survival curves. Beneath each treated group incidence is the p-value corresponding to the Cox test pairwise comparisons between the treated group and control group.
4) Three p-values are tabulated for Tarone's test. The first value is for a two-tailed test of trend. The second figure is for a one-tailed test for positive trend. The third value is the p-value for the test of departure from a linear trend.

Table 25

Incidence (%) of vascular endothelial tumours among female CD-1 mice from 104 weeks oncogenicity studies

	Study reference number CDM032*		.....This study.....				
			Females				
Group	A	B	1#	2	3	4	5
Level (% w/w)			0	0	0.03	0.1	0.3
Vascular endothelial tumours	5(10)	7(13)	6(12)	1(2)	3(6)	6(12)	7[a](14)
Number of animals examined	52	52	50	50	50	50	50

* Historical control data were selected to ensure that the conditions of animal husbandry were similar to those used for this study
a Significantly different from controls, P < 0.05
\# Selected tissues only (liver, ovaries, skin, spleen, uterus, uterine cervix)
A and B are used to identify control groups for studies with two such groups

Table 26

Group distribution of microscopic findings in treated skin

	Males				Females			
Group	2	3	4	5	2	3	4	5
Level (% w/w)	0	0.03	0.1	0.3	0	0.03	0.1	0.3
Skin treated x 4 Number examined	50	50	50	50	50	50	50	50
- Acanthosis	4	50[c]	49[c]	48[c]	3	50[c]	50[c]	50[c]
- Hyperkeratosis	1	26[c]	38[c]	44[c]	0	31[c]	44[c]	47[c]
- Scab(s)	3	23[c]	32[c]	38[c]	0	24[c]	23[c]	36[c]
- Ulcer(s)	1	7	14[c]	24[c]	1	1	6	10[b]
- Diffuse subcutaneous inflammation collagen deposition	0	27[c]	37[c]	43[c]	0	38[c]	43[c]	42[c]
- Increased superficial follicles	0	1	1	8[b]	0	0	3	7[a]
- Atrophy of glandular and/or follicular structures	1	12[b]	19[c]	26[c]	0	3	9[b]	12[c]

a Significantly different from vehicle controls, P < 0.05
b Significantly different from vehicle controls, P < 0.01
c Significantly different from vehicle controls, P < 0.001

Table 27

Group distribution and severity of acanthosis in treated skin

	Males				Females			
Group	2	3	4	5	2	3	4	5
Level (% w/w)	0	0.03	0.1	0.3	0	0.03	0.1	0.3
Skin treated x 4 Number examined	50	50	50	50	50	50	50	50
Acanthosis								
- minimal	0	1	1	0	1	1	1	0
- slight	4	18	8	5	2	21	10	2
- moderate	0	30	39	36	0	28	33	38
- marked	0	1	1	7	0	0	6	10

Table 28
Intercurrent Mortality Rates
Male Mice

Weeks	Neg. Cont.			Veh. Cont.			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	2	4	50	6	12	50	8	16	50	8	16	50	14	28
51-80	48	7	14.5	44	8	18.2	42	9	21.4	42	11	26.2	36	14	38.8
81-104 /81-98	41	17	41.4	36	9	25	33	11	33.3	31	16	51.6	22	6	27.2
Term.	24			27			22			15			16		

Female Mice

Weeks	Neg. Cont.			Veh. Cont.			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	3	6	50	7	14	50	2	4	50	5	10	50	7	14
51-80	47	9	19.1	43	6	13.9	48	8	16.6	45	17	37.7	43	11	25.6
81-104 /81-101	38	16	42.1	37	13	35.1	40	19	47.5	28	9	32.1	32	17	53.1
Term.	22			24			21			19			15		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 29
Tumor Incidence Rates
Female Mice, Spleen Hemangiosarcoma and Hemangioma

Weeks	Neg. Control		Veh. Control		Low		Medium		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	3	0	7	0	2	0	5	0	7
51-80	0	9	0	6	0	8	0	17	0	11
81-104/ 81-101	1	16	0	13	0	19	1	9	2	17
terminal	0	22	0	24	1	21	0	19	1	15
Total	1	50	0	50	1	50	1	50	3	50

C1: p-value = 0.0962
C2: p-value = 0.0372
C1+C2: p-value = 0.0405

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

NAME OF COMPANY: GALDERMA

APPENDIX I ($ PAGES)

SUMMARY TABLE

REFERENCE TO

/

PAGE NUMBER

NAME OF FINISHED PRODUCT: *DIFFERIN GEL*

NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*

REPORT DATE: *1) 22 APRIL 1992 - 2) 13 APRIL 1992*

REPORT NUMBER: *1) MD/92070 - 2) 91/CID053/1021*

STUDY PERIOD (YEARS): *1989 1990-1991*

REFERRING TO DOCUMENTATION

VOLUME: PAGE: TO:

ADDENDUM NO:

ONCOGENIC/CARCINOGENIC POTENTIAL

TUMOUR DATA

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(1) CONTROL		(2) (CD271)		(3) (CD271)		(4) (CD271)	
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		60	60	60	60	60	60	60	60
ORGAN	IDENTIFICATION OF THE TUMOUR								
ADRENAL									
CORTEX	CORTICAL ADENOMA	0	0	0	1	0	0	0	0
ADRENAL									
MEDULLA	MALIGNANT PHAEOCHROMOCYTOMA	2	1	3	1	0	2	3	3
	BENIGN PHAEOCHROMOCYTOMA	7	6	9	3	10	6	18*	3
BRAIN	NUMBER EVALUATED IF LESS THAN 60				59				
	MALIGNANT GRANULAR CELL TUMOUR	3	1	1	0	0	0	3	0
	MALIGNANT ASTROCYTOMA	0	0	0	0	1	0	0	0
COLON	NUMBER EVALUATED IF LESS THAN 60	59				59			
	CARCINOMA	0	0	0	0	1	0	0	0
DUO-	NUMBER EVALUATED IF LESS THAN 60	59		59		59	59		
DENUM	CARCINOMA	0	0	0	0	0	1	1	0
JEJUNUM	NUMBER EVALUATED IF LESS THAN 60		59	59	59	57			
	CARCINOMA	0	0	0	0	0	0	1	0
	LEIOMYOSARCOMA	0	0	0	0	1	0	0	0
LIVER	HEPATOCELLULAR CARCINOMA	1	0	3	1	1	0	3	1
	HEPATOCELLULAR ADENOMA	0	0	0	0	0	1	0	0
MAMMARY	NUMBER EVALUATED IF LESS THAN 60		58		59				59
TISSUE	FIBROADENOMA	0	0	0	1	0	1	0	0
CAUDAL									
MES	NUMBER EVALUATED IF LESS THAN 60	59		59					
LYMPH	HAEMANGIOMA	0	0	0	0	0	0	1	0
NODES									
OVARIES	GRANULOSA-THECA CELL CARCINOMA	N/A	0	N/A	0	N/A	1	N/A	0

* $p < 0.05$. N/A - Not Applicable.
MES - MESENTERIC

CIRD TO.3017 A

5 07286

GALDERMA	REFERENCE TO. / PAGE NUMBER
NAME OF FINISHED PRODUCT: *DIFFERIN GEL*	
NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*	REPORT DATE: *1) 22 APRIL 1992 - 2) 13 APRIL 1992* REPORT NUMBER: *1) MD/92070 - 2) 91/CID053/1021* STUDY PERIOD (YEARS): *1989 1990-1991*
ONCOGENIC/CARCINOGENIC POTENTIAL TUMOUR DATA	REFERRING TO DOCUMENTATION VOLUME: PAGE: TO: ADDENDUM NO:

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(1) CONTROL		(2) (CD271)		(3) (CD271)		(4) (CD271)	
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		60	60	60	60	60	60	60	60
ORGAN	IDENTIFICATION OF THE TUMOUR								
PANCREAS	NUMBER EVALUATED IF LESS THAN 60		59	59				59	
	ISLET CELL CARCINOMA	1	0	4	1	4	1	4	0
	ISLET CELL ADENOMA	2	1	4	1	2	1	5	2
	EXOCRINE CELL ADENOMA	0	0	0	0	1	0	0	0
PARA-	NUMBER EVALUATED IF LESS THAN 60	53	53	51	52	54	58	56	52
THYROIDS	ADENOMA	3	1	4	3	3	2	2	0
PITUITARY	NUMBER EVALUATED IF LESS THAN 60		59		59				
	CARCINOMA	0	0	0	1	1	0	1	0
	MALIGNANT GRANULAR CELL TUMOUR	0	0	1	0	0	0	0	0
	ADENOMA	30	46	25	45	24	45	25	45
PROSTATE	NUMBER EVALUATED IF LESS THAN 60		NIA		NIA		NIA	59	NIA
	ADENOCARCINOMA	0	NIA	0	NIA	1	NIA	0	NIA
RECTUM	NUMBER EVALUATED IF LESS THAN 60					58			
	LEIOMYOSARCOMA	0	0	1	0	0	0	0	0
SEMINAL	ADENOCARCINOMA	0	NIA	1	NIA	0	NIA	0	NIA
VESICLES									
SKELETAL	SARCOMA	0	0	0	1	0	0	0	0
MUSCLE									
TESTES	BENIGN INTERSTITIAL CELL TUMOUR	2	NIA	2	NIA	2	NIA	2	NIA
THYMUS	NUMBER EVALUATED IF LESS THAN 60	56	55	51	57	57	51	57	55
	ADENOCARCINOMA OF THYROGLOSSAL DUCT	0	0	0	0	0	0	1	0
	THYOMA	0	2	0	0	0	0	0	0

* P < 0.05. N/A - Not Applicable

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NAME OF COMPANY: GALDERMA

NAME OF FINISHED PRODUCT: *DIFFERIN GEL*

NAME OF ACTIVE INGREDIENTS: *ADAPALENE*

SUMMARY TABLE

REFERENCE TO

/

PAGE NUMBER

REPORT DATE: *1) 22 APRIL 1992 - 2) 13 APRIL 1992*

REPORT NUMBER: *1) MD/92070 - 2) 91/CID0531/021*

STUDY PERIOD (YEARS): *1989 1990-1991*

REFERRING TO DOCUMENTATION

VOLUME: PAGE: TO:

ADDENDUM NO:

ONCOGENIC/CARCINOGENIC POTENTIAL

TUMOUR DATA

NUMBER OF TUMOURS (ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(1) CONTROL		(2) (CD271)		(3) (CD271)		(4) (CD271)	
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		60	60	60	60	60	60	60	60
ORGAN	IDENTIFICATION OF THE TUMOUR								
THYROIDS	NUMBER EVALUATED IF LESS THAN 60	56		58	59	59		57	
	FOLLICULAR CELL CARCINOMA	0	0	2	0	2	1	0	1
	FOLLICULAR CELL ADENOMA	2	0	1	1	0	0	1	4
	PARAFOLLICULAR CELL CARCINOMA	1	1	2	0	2	3	3	0
	PARAFOLLICULAR CELL ADENOMA	5	2	1	4	5	5	0	4
URINARY	NUMBER EVALUATED IF LESS THAN 60							59	
BLADDER	TRANSITIONAL CELL PAPILLOMA	0	0	0	1	0	0	1	0
UTERUS	NUMBER EVALUATED IF LESS THAN 60	N/A		N/A		N/A		N/A	59
	ADENOCARCINOMA	N/A	0	N/A	0	N/A	2	N/A	1
	FIBROMA	N/A	0	N/A	0	N/A	1	N/A	0
VAGINA	NUMBER EVALUATED IF LESS THAN 60	N/A		N/A		N/A		N/A	59
	SQUAMOUS PAPILLOMA	N/A	1	N/A	0	N/A	0	N/A	0
ABDOMEN	NUMBER EVALUATED IF LESS THAN 60	1	0	0	0	1	0	1	0
	SARCOMA	1	N/A	N/A	N/A	0	N/A	1	N/A
EYE RIGHT	NUMBER EVALUATED IF LESS THAN 60	6	6	13	2	8	6	6	1
	SCHWANNOMA	1	0	0	0	0	0	0	0
FOOT	NUMBER EVALUATED IF LESS THAN 60	6	4	3	2	4	3	4	3
	SARCOMA	1	0	0	0	0	0	1	0
	PAPILLOMA	0	0	0	0	0	0	1	0
HAEM-	MONOCYTIC LEUKAEMIA	1	0	2	2	2	1	4	0
OPOIETIC	MALIGNANT LYMPHOMA	1	0	1	0	2	1	0	0
TUMOUR	HISTIOCYTIC SARCOMA	0	0	0	0	0	2	2	0

* $p < 0.05$. N/A - Not Applicable

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NAME OF COMPANY: GALDERMA

NAME OF FINISHED PRODUCT: *DIFFERIN GEL*

SUMMARY TABLE

REFERENCE TO

/

PAGE NUMBER

NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*

REPORT DATE: *1) 22 APRIL 1992 - 2) 13 APRIL 1992*

REPORT NUMBER: *1) MD.92070 - 2) 91/CID053/1021*

STUDY PERIOD (YEARS): *1989 1990-1991*

ONCOGENIC/CARCINOGENIC POTENTIAL

TUMOUR DATA

REFERRING TO DOCUMENTATION

VOLUME: PAGE: TO:

ADDENDUM NO:

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(1) CONTROL		(2) (CD271)		(3) (CD271)		(4) (CD271)	
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		60	60	60	60	60	60	60	60
ORGAN	IDENTIFICATION OF THE TUMOUR								
MAMMARY	NUMBER EVALUATED IF LESS THAN 60	7	44	3	46	0	45	2	46
TISSUE	CARCINOMA	0	10	0	4	NIA	9	0	7
OTHER	FIBROADENOMA	5	42	3	41	NIA	40	2	43
MISCELL-	NUMBER EVALUATED IF LESS THAN 60	0	1	1	0	0	0	0	0
ANEOUS	CHORDOMA	NIA	1	1	NIA	NIA	NIA	NIA	NIA
MUSCULO -	NUMBER EVALUATED IF LESS THAN 60	3	0	1	0	1	0	0	0
SKELETAL	OSTEOSARCOMA	3	NIA	0	NIA	0	NIA	NIA	NIA
SALIVARY	NUMBER EVALUATED IF LESS THAN 60	0	0	0	1	0	0	0	0
GLAND	MALIGNANT CARCINOMA	NIA	NIA	NIA	1	NIA	NIA	NIA	NIA
OTHER									
SKIN	NUMBER EVALUATED IF LESS THAN 60	31	51	36	55	20	50	35	51
OTHER	SARCOMA	4	1	4	1	3	2	3	0
	CARCINOMA	0	0	1	2	0	0	1	0
	MYOEPITHELIOMA	0	1	0	0	0	0	1	0
	ZYMBAL'S GLAND CARCINOMA	0	0	0	0	0	0	0	1
	PAPILLOMA	3	1	3	0	2	1	3	0
	KERATOACANTHOMA	2	0	4	0	3	0	6	0
	BENIGN BASAL CELL TUMOUR	0	0	1	0	1	0	1	0
	SEBACEOUS ADENOMA	1	0	0	0	0	0	0	0
	LIPOMA	3	1	7	0	2	1	4	0
	FIBROMA	4	1	5	1	0	4	4	3
TAIL	NUMBER EVALUATED IF LESS THAN 60	1	1	2	1	1	1	2	1
	PAPILLOMA	1	0	2	0	0	0	1	0

* $p < 0.05$. N/A - Not Applicable

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NAME OF COMPANY: GALDERMA

APPENDIX II (8 pages)

SUMMARY TABLE

REFERENCE TO

/

PAGE NUMBER

NAME OF FINISHED PRODUCT: *DIFFERIN GEL*

NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*

REPORT DATE: *April 22, 1992* *March 3, 1992*

REPORT NUMBER: *MD192071* *91ICID03710644*

STUDY PERIOD (YEARS): *1989 - 1990 - 1991*

REFERRING TO DOCUMENTATION

VOLUME: PAGE: TO:

ADDENDUM NO:

ONCOGENIC/CARCINOGENIC POTENTIAL

TUMOUR DATA

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(2) VEHICLE Control		(3) CD271 AQUEOUS GEL		(4) CD271 AQUEOUS GEL		(5) CD271 AQUEOUS GEL	
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		50	50	50	50	50	50	50	50
ORGAN	IDENTIFICATION OF THE TUMOUR								
ADRENAL -	NUMBER EVALUATED IF LESS THAN 50			49	49			47	
CORTEX	CORTICAL ADENOMA	1	1	3	0	2	0	2	0
	SPINDLE CELL TUMOR (BENIGN)	0	1	0	1	1	0	0	0
ADRENAL -	NUMBER EVALUATED IF LESS THAN 50	49		49	49			47	
MEDULLA	PHAEOCHROMOCYTOMA	0	0	0	1	0	1	0	0
KIDNEYS	NUMBER EVALUATED IF LESS THAN 50								
	RENAL CARCINOMA	0	0	0	0	1	0	0	0
	HAEMANGIOSARCOMA	1	0	0	0	0	0	0	0
LIVER	HEPATOCELLULAR CARCINOMA	2	0	9*	1	5	0	3	0
	HEPATOCELLULAR ADENOMA	0	0	0	2	2	0	1	0
	HAEMANGIOSARCOMA	2	1	3	2	2	1	2	1
	HAEMANGIOMA	0	0	2	0	1	1	0	0
LUNGS	NUMBER EVALUATED IF LESS THAN 50			32	34	39	35		
	PULMONARY CARCINOMA	8	5	5	2	7	3	4	0
	PULMONARY ADENOMA	3	7	3	4	6	0	2	2
OESOPHA-	NUMBER EVALUATED IF LESS THAN 50		49	28	29	35	31		
GUS	SQUAMOUS CELL PAPILLOMA	0	0	0	0	0	0	1	0
OVARIES	NUMBER EVALUATED IF LESS THAN 50	N/A		N/A	42	N/A	43	N/A	
	GRANULOSA-THECA CELL CARCINOMA	N/A	0	N/A	1	N/A	0	N/A	1
	ADENOMA	N/A	4	N/A	1	N/A	0	N/A	3
	HAEMANGIOSARCOMA	N/A	0	N/A	0	N/A	0	N/A	1
	LUTEOMA	N/A	0	N/A	0	N/A	0	N/A	0
PARA-	NUMBER EVALUATED IF LESS THAN 50	38	39	15	21	25	27	40	44
THYROIDS	ADENOMA	0	0	0	0	0	0	0	1

* $p < 0.05$. N/A Not Applicable

NAME OF COMPANY: GALDERMA

NAME OF FINISHED PRODUCT: *DIFFERIN GEL*

REFERENCE TO / PAGE NUMBER

NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*

REPORT DATE: *April 22, 1992* *March 3, 1992*

REPORT NUMBER: *MD192071* *91ICID03710644*

STUDY PERIOD (YEARS): *1989 - 1990 - 1991*

REFERRING TO DOCUMENTATION

VOLUME: PAGE: TO:

ADDENDUM NO.:

ONCOGENIC/CARCINOGENIC POTENTIAL

TUMOUR DATA

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(2) VEHICLE Control		(3) CD271 AQUEOUS GEL		(4) CD271 AQUEOUS GEL		(5) CD271 AQUEOUS GEL	
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		50	50	50	50	50	50	50	50
ORGAN	IDENTIFICATION OF THE TUMOUR								
PANCREAS	NUMBER EVALUATED IF LESS THAN 50			28	28	36	31		
	ISLET CELL ADENOMA	1	0	0	0	0	0	0	0
PITUITARY	NUMBER EVALUATED IF LESS THAN 50	49	49	28	29	35	30	49	
	ADENOMA	0	0	0	1	0	1	0	0
PROSTATE	NUMBER EVALUATED IF LESS THAN 50	49	NIA	27	NIA	32	NIA		NIA
	ADENOCARCINOMA	0	NIA	0	NIA	0	NIA	1	[illegible]
SKIN -	NUMBER EVALUATED IF LESS THAN 50								
TREATED	SARCOMA	1	0	0	1	0	0	0	0
	PAPILLOMA	0	0	0	0	0	1	0	0
SPLEEN	NUMBER EVALUATED IF LESS THAN 50	49				49			
	HAEMANGIOSARCOMA	0	0	1	1	1	1	1	2
	HAEMANGIOMA	0	0	0	0	0	0	1	1
SUBMAN.-	NUMBER EVALUATED IF LESS THAN 50			28	28	35	31		
SALIVARY-	CARCINOMA	0	0	0	0	0	0	0	0
GLAND (L)									
TESTES	INTERSTITIAL CELL TUMOR (BENIGN)	1	NIA	0	NIA	1	NIA	0	NI.
THYMUS	NUMBER EVALUATED IF LESS THAN 50	44	48	28	29	29	30	44	46
	THYPOGLOSSAL DUCT CARCINOMA	0	1	0	0	0	0	0	0
	THYMOMA	0	0	0	0	0	0	0	0
UTERINE -	NUMBER EVALUATED IF LESS THAN 50	NIA		NIA	29	NIA	28	NIA	4[illegible]
CERVIX	LEIOMYOMA	NIA	0	NIA	0	NIA	0	NIA	1
	LEIOMYOSARCOMA	NIA	0	NIA	1	NIA	0	NIA	0
UTERUS	NUMBER EVALUATED IF LESS THAN 50	NIA		NIA	49	NIA		NIA	
	LEIOMYOSARCOMA	NIA	2	NIA	2	NIA	2	NIA	

* $p < 0.05$. N/A Not Applicable. (L) Left

NAME OF COMPANY: GALDERMA	SUMMARY TABLE REFERENCE TO / PAGE NUMBER
NAME OF FINISHED PRODUCT: *DIFFERIN GEL*	
NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*	REPORT DATE: *April 22, 1992* — *March 3, 1992* REPORT NUMBER: *MD192071* — *91/CID03710644* STUDY PERIOD (YEARS): *1989 - 1990 - 1991*
ONCOGENIC/CARCINOGENIC POTENTIAL TUMOUR DATA	REFERRING TO DOCUMENTATION VOLUME: PAGE: TO: ADDENDUM NO:

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED

(WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(1) CONTROL (CLIPPED ONLY)							
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		*0*	*50*						
ORGAN	IDENTIFICATION OF THE TUMOUR								
PANCREAS	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*4*						
	ISLET CELL ADENOMA	*N/A*	*0*						
PITUITARY	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*2*						
	ADENOMA	*N/A*	*2*						
PROSTATE	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*N/A*						
	ADENOCARCINOMA	*N/A*	*N/A*						
SKIN -	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*2*						
TREATED	*SARCOMA*	*N/A*	*0*						
	PAPILLOMA	*N/A*	*0*						
SPLEEN	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*							
	HAEMANGIOSARCOMA	*N/A*	*1*						
	HAEMANGIOMA	*N/A*	*0*						
SUBMAN.-	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*1*						
SALIVARY-	*CARCINOMA*	*N/A*	*1*						
GLAND (L)									
TESTES	*INTERSTITIAL CELL TUMOR (BENIGN)*	*N/A*	*N/A*						
THYMUS	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*6*						
	THYPOGLOSSAL DUCT CARCINOMA	*N/A*	*0*						
	THYMOMA	*N/A*	*1*						
UTERINE -	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*							
CERVIX	*LEIOMYOMA*	*N/A*	*0*						
	LEIOMYOSARCOMA	*N/A*	*0*						
UTERUS	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*0*						
	LEIOMYOSARCOMA	*N/A*	*4*						

* $p < 0.05$. N/A Not Applicable. (L) Left

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NAME OF COMPANY: GALDERMA

NAME OF FINISHED PRODUCT: *DIFFERIN GEL*

REFERENCE TO / PAGE NUMBER

NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*

REPORT DATE: *April 22, 1992* *March 3, 1992*

REPORT NUMBER: *MD192071* *91ICID03710644*

STUDY PERIOD (YEARS): *1989 - 1990 - 1991*

REFERRING TO DOCUMENTATION

VOLUME: PAGE: TO:

ADDENDUM NO:

ONCOGENIC/CARCINOGENIC POTENTIAL

TUMOUR DATA

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(2) VEHICLE Control		(3) CD271 AQUEOUS GEL		(4) CD271 AQUEOUS GEL		(5) CD271 AQUEOUS GEL	
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		50	50	50	50	50	50	50	50
ORGAN	IDENTIFICATION OF THE TUMOUR								
UTERUS	NUMBER EVALUATED IF LESS THAN 50	N/A		N/A	49	N/A		N/A	
	ENDOMETRIAL SARCOMA	N/A	1	N/A	0	N/A	0	N/A	1
	ADENOCARCINOMA	N/A	0	N/A	1	N/A	1	N/A	0
	HAEMANGIOSARCOMA	N/A	0	N/A	0	N/A	1	N/A	1
	HAEMANGIOMA	N/A	0	N/A	0	N/A	1	N/A	1
	LEIOMYOMA	N/A	0	N/A	1	N/A	0	N/A	0
ABDOMEN	NUMBER EVALUATED IF LESS THAN 50	0	3	0	1	0	0	0	1
	SARCOMA	N/A	1	N/A	0	N/A	N/A	N/A	1
HAEMO-	MALIGNANT LYMPHOMA	7	5	8	11	10	9	5	10
POIETIC -	HISTIOCYTIC SARCOMA	1	5	0	1	2	4	0	1
TUMOUR	GRANULOCYTIC LEUKAEMIA	0	0	0	0	0	1	0	0
HARD-	NUMBER EVALUATED IF LESS THAN 50	20	29	20	26	10	23	11	28
ERIAN -	ADENOMA	3	0	2	3	2	0	0	0
GLAND (L)									
HARD-	NUMBER EVALUATED IF LESS THAN 50	20	29	20	26	9	23	11	28
ERIAN -	CARCINOMA	0	1	0	0	0	0	0	0
GLAND (R)	ADENOMA	1	1	2	0	1	1	0	1
MAMMARY	NUMBER EVALUATED IF LESS THAN 50	1	1	0	5	0	2	0	1
OTHER	ADENOCARCINOMA	0	1	N/A	4	N/A	2	N/A	1
MUSCULO -	NUMBER EVALUATED IF LESS THAN 50	1	2	0	1	1	0	0	1
SKELETAL	OSTEOSARCOMA	1	1	N/A	0	0	N/A	N/A	0
	SARCOMA	0	1	N/A	0	0	N/A	N/A	0
SKIN -	NUMBER EVALUATED IF LESS THAN 50	9	12	16	14	24	20	32	22
OTHER	SARCOMA	1	1	0	0	1	0	0	0

* $p < 0.05$. N/A Not Applicable. (L) Left. (R) Right

NAME OF COMPANY: GALDERMA	SUMMARY TABLE REFERENCE TO / PAGE NUMBER
NAME OF FINISHED PRODUCT: *DIFFERIN GEL*	
NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*	REPORT DATE: *April 22, 1992* *March 3, 1992*
	REPORT NUMBER: *MD/92071* *91/CID03710644*
	STUDY PERIOD (YEARS): *1989 - 1990 - 1991*
ONCOGENIC/CARCINOGENIC POTENTIAL	REFERRING TO DOCUMENTATION
TUMOUR DATA	VOLUME: PAGE: TO:
	ADDENDUM NO:

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)		FREQUENCY ACCORDING TO DOSE AND SEX (n)							
		(1) CONTROL (CLIPPED ONLY)							
BIOMETRICAL EVALUATION: YES [+] NO [ ]		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		*0*	*50*						
ORGAN	IDENTIFICATION OF THE TUMOUR								
UTERUS	*NUMBER EVALUATED IF LESS THAN 50*	*NIA*							
	ENDOMETRIAL SARCOMA	*NIA*	*2*						
	ADENOCARCINOMA	*NIA*	*0*						
	HAEMANGIOSARCOMA	*NIA*	*1*						
	HAEMANGIOMA	*NIA*	*1*						
	LEIOMYOMA	*NIA*	*0*						
ABDOMEN	*NUMBER EVALUATED IF LESS THAN 50*	*NIA*	*0*						
	SARCOMA	*NIA*	*NIA*						
HAEMO-	*MALIGNANT LYMPHOMA*	*NIA*	*9*						
POIETIC -	*HISTIOCYTIC SARCOMA*	*NIA*	*3*						
TUMOUR	*GRANULOCYTIC LEUKAEMIA*	*NIA*	*0*						
HARD-	*NUMBER EVALUATED IF LESS THAN 50*	*NIA*	*1*						
ERIAN -	*ADENOMA*	*NIA*	*0*						
GLAND (L)									
HARD-	*NUMBER EVALUATED IF LESS THAN 50*	*NIA*	*1*						
ERIAN -	*CARCINOMA*	*NIA*	*0*						
GLAND (R)	*ADENOMA*	*NIA*	*0*						
MAMMARY	*NUMBER EVALUATED IF LESS THAN 50*	*NIA*	*3*						
OTHER	*ADENOCARCINOMA*	*NIA*	*3*						
MUSCULO -	*NUMBER EVALUATED IF LESS THAN 50*	*NIA*	*0*						
SKELETAL	*OSTEOSARCOMA*	*NIA*	*NIA*						
	SARCOMA	*NIA*	*NIA*						
SKIN -	*NUMBER EVALUATED IF LESS THAN 50*	*NIA*	*21*						
OTHER	*SARCOMA*	*NIA*	*4*						

* $p < 0.05$. - No animals evaluated. (L) Left, (R) Right

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NAME OF COMPANY: GALDERMA

NAME OF FINISHED PRODUCT: *DIFFERIN GEL*

REFERENCE TO / PAGE NUMBER

NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*

REPORT DATE: *April 22, 1992* *March 3, 1992*

REPORT NUMBER: *MD192071* *91/CID03710644*

STUDY PERIOD (YEARS): *1989 - 1990 - 1991*

REFERRING TO DOCUMENTATION

VOLUME: PAGE: TO:

ADDENDUM NO:

ONCOGENIC/CARCINOGENIC POTENTIAL

TUMOUR DATA

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)

BIOMETRICAL EVALUATION: YES [+] NO [ ]

		FREQUENCY ACCORDING TO DOSE AND SEX (a)							
		(2) VEHICLE Control		(3) CD271 AQUEOUS GEL		(4) CD271 AQUEOUS GEL		(5) CD271 AQUEOUS GEL	
		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		50	50	50	50	50	50	50	50
ORGAN	IDENTIFICATION OF THE TUMOUR								
SKIN -	NUMBER EVALUATED IF LESS THAN 50	9	12	16	14	24	20	32	22
OTHER	HAEMANGIOSARCOMA	0	0	0	0	0	1	0	0
	PAPILLOMA	0	0	0	0	0	1	0	0
	BASAL CELL TUMOUR (BENIGN)	0	0	0	0	0	0	0	1
TAIL	NUMBER EVALUATED IF LESS THAN 50	4	3	2	0	0	1	3	1
	SARCOMA	0	0	1	N/A	N/A	0	0	0

* $p < 0.05$. N/A Not Applicable

NAME OF COMPANY: GALDERMA	SUMMARY TABLE REFERENCE TO / PAGE NUMBER	(For Authority use only)
NAME OF FINISHED PRODUCT: *DIFFERIN GEL*		
NAME OF ACTIVE INGREDIENT(S): *ADAPALENE*	REPORT DATE: *April 22, 1992*	*March 3, 1992*
	REPORT NUMBER: *MD192071*	*91/CID037/0644*
	STUDY PERIOD (YEARS): *1989 - 1990 - 1991*	
ONCOGENIC/CARCINOGENIC POTENTIAL	REFERRING TO DOCUMENTATION	
TUMOUR DATA	VOLUME: PAGE: TO:	
	ADDENDUM NO:	

NUMBER OF TUMOURS IN ALL ANIMALS WHICH WERE EVALUATED (WITHOUT CONSIDERATION OF THE CAUSES AND RELEVANCE)		FREQUENCY ACCORDING TO DOSE AND SEX (s)							
		(1) CONTROL (CLIPPED ONLY)							
BIOMETRICAL EVALUATION: YES [+] NO [ ]		M	F	M	F	M	F	M	F
NUMBER OF ANIMALS EVALUATED		*0*	*50*						
ORGAN	IDENTIFICATION OF THE TUMOUR								
SKIN -	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*21*						
OTHER	*HAEMANGIOSARCOMA*	*N/A*	*1*						
	PAPILLOMA	*N/A*	*2*						
	BASAL CELL TUMOUR (BENIGN)	*N/A*	*0*						
TAIL	*NUMBER EVALUATED IF LESS THAN 50*	*N/A*	*0*						
	SARCOMA	*N/A*	*N/A*						

* $p < 0.05$. N/A Not Applicable

5-04856

In the 78-week rat chronic toxicity phase, results of tumor data analyses showed that there was a significant positive linear trend in adrenal benign and malignant pheochromocytomas (p = 0.0003) in male rats. Noted that there are only 20 animals per sex/group in this study. The results of tumor data analyses of 104-week rat oncogenicity study showed that there were significant positive linear trends in thyroids follicular cell adenoma and carcinoma combined (p = 0.0049) in female rats and in adrenal benign and malignant pheochromocytomas (p = 0.0051) in male rats. There were marginally significant positive linear trends in H'poietic histiocytic sarcoma (p = 0.0696) and in H'poietic monocytic leukaemia (p = 0.0696) in male rats. Similar results were found when the tumor data of both rat studies were combined.

In the mouse study, results of the tumor data analyses showed that there was a significant positive linear trend in the spleen hemangicsarcoma and hemangioma (p = 0.0372) in female mice when vehicle ɔntrol, low, medium, and high dose groups were considered.

Chem

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JUN 9 1993

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-338 DATE REVIEWED: 5-5-93

REVIEW #: 1 REVIEWER: J. Timper

SUBMISSION TYPE: Original NDA submission

DOCUMENT DATE: CDER DATE:

On December 14, 1992 (CDER 12/17/93) the applicant provided the **Pre-NDA submission** containing the chemistry, manufacturing, and controls section of the NDA. The submission dated 3/19/93 (CDER 3/29/93) is recognized as the complete submission.

ASSIGNED DATE Pre-submission: 12/22/93

NAME & ADDRESS OF APPLICANT:

Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516
FAX 817 763-5863

CONTACT:

ATTN: Christine E. Shank
Manager, Regulatory Affairs
(817) 551-8516
FAX (817) 763-5863

DRUG PRODUCT NAME

Proprietary: Differin Solution, 0.1%
Established: Adapalene
Code #: CD 271 Topical; AL02866

PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of acne vulgaris

DOSAGE FORM: Topical Solution STRENGTHS: 0.1% (1mg/mL)

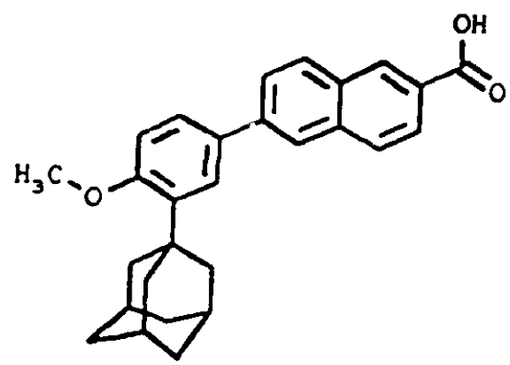
ROUTE OF ADMINISTRATION: Topical Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Adapalene
CAS-106685-40-9; code names: CD 271; AL02866

Molecular Formula: $C_{28}H_{28}O_3$
Molecular Weight: 412.52
Chemical Name:

(1) 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid



SUPPORTING DOCUMENTS:

IND
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IND
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IND
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RELATED DOCUMENTS:

DMF
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CONSULTS: Environmental Assessment

REMARKS:

1. Method validation required;
2. Type 1-S drug;
3. Review chemist to participate in the inspection;
4. Letter authorization for the active drug substance DMF dated 9-3-92, received 10-1-92, referencing Owen Galderma Inc., 6201 South Freeway, Fort Worth, Texas, provided by to review

CONCLUSIONS & RECOMMENDATIONS:

Recommend nonapproval at the current time. Deficiencies are cited or operations pertaining to review sections are not completed in the following: Stability declaration. method validation is incomplete, environmental assessment consult is incomplete, inspection is incomplete, the labeling requires revision, laboratory controls.

	YES	NO
DRAFT LETTER	x	—
TELECONS	—	x

JT 5-5-93

J. Timper

cc: Org. NDA 20-338
HFD-520/Division File
HFD-520/DeCamp/SUPVCHEM JD 6/8/93
HFD-520/Timper/CHEM 5/5/93
HFD-520/Rand/MO
HFD-520/Browder/PHARM
HFD-520/Sheldon/MICRO
HFD-520/Cook/CSO
HFD-102/CKumkumian [#1 only]
HFC-130/JAllen

MMC 6/9/93

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-338 **DATE REVIEWED:** 7-6-93
Date of this memo: 5/31/94

regarding: REVIEW #: 2 **REVIEWER:** J. Timper

SUBMISSION TYPE:

PLEASE NOTE THAT REVIEW #2 BECAME SUPERFLUOUS BY INFORMATION SUBMITTED BY THE FIRM RESPONDING TO FAILURE OF THE PRODUCT SPECIFIC INSPECTION at DPT; ALL ISSUES WERE noted IN THE SEQUEL, REVIEW #3.

NAME & ADDRESS OF APPLICANT:

Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516
FAX 817 763-5863

DRUG PRODUCT NAME

Proprietary: Differin Solution, 0.1%
Established: Adapalene
Code #: CD 271 Topical; AL02866

J. Timper 5/31/94

cc: Org. NDA 20-338
HFD-520/Division File 6/3/94

SEP 30 1993

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-338 **DATE REVIEWED:** 9-7-93

REVIEW #: 3 **REVIEWER:** J. Timper

SUBMISSION TYPE:

The review #2, completed 7/6/93, was based on the product specific inspection at DPT Laboratories, San Antonio, Texas; the inspection results was presented to the firm at the time the inspection was completed, 7/2/93, by Mr. Joel Martinez and this reviewer. The FDA 483 cited the failure of that firm, manufacturer of the drug product, to meet satisfactory controls with regard to chemistry and manufacturing. (See "REMARKS" below for summary statement quoted from the Form FDA 481(e)-CG, the recommendation for non-approval of NDA.)

The formal recommendation for non-approval, Form FDA 481(e)-CG, signed by the supervisory inspector of the San Antonio resident post, Mr. John W. Davis, Jr. was issued dated 7/20/93.

The response to the FDA 483 was submitted to the file dated 8/12/93, received 8/16/93. This submission is the subject of this review; the observations of this review will be communicated to the inspector in the San Antonio resident post since the FDA 483 evaluation for compliance is the prerogative of the inspector.

DOCUMENT DATE; CDER DATE:

On December 14, 1992 (CDER 12/17/93) the applicant provided the **Pre-NDA submission** containing the chemistry, manufacturing, and controls section of the NDA. The submission dated 3/19/93 (CDER 3/29/93) is recognized as the complete submission.

The response to the FDA 483 was submitted to the file dated 8/12/93, received 8/16/93. This submission is the subject of this review

ASSIGNED DATE 8/17/93

NAME & ADDRESS OF APPLICANT:

Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516
FAX 817 763-5863

CONTACT:

ATTN: Christine E. Shank
Manager, Regulatory Affairs
(817) 551-8516
FAX (817) 763-5863

DRUG PRODUCT NAME

Proprietary: Differin Solution, 0.1%
Established: Adapalene
Code #: CD 271 Topical; AL02866

PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of acne vulgaris

DOSAGE FORM: Topical Solution **STRENGTHS:** 0.1% (1mg/mL)

ROUTE OF ADMINISTRATION: Topical **Rx/OTC:** Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Adapalene
CAS-106685-40-9; code names: CD 271; AL02866

Molecular Formula: $C_{28}H_{28}O_3$
Molecular Weight: 412.52
Chemical Name:

(1) 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

SUPPORTING DOCUMENTS:

IND . . . . . Owen/Galderma Laboratories, Inc.
. . CD 271 Topical Solution (adapalene)

IND . . . . . Owen/Galderma Laboratories, Inc.
. . CD 271 Topical Gel (adapalene)

IND . . . . . Owen/Galderma Laboratories, Inc.
. . CD 271 Topical Cream (adapalene)

RELATED DOCUMENTS:

DMF
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DMF
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DMF DPT Laboratories Inc.,
. . San Antonio, TX

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CONSULTS:

Environmental Assessment: Inadequate

The current status of the Environmental Assessment for the Topical Gel, NDA 20-338 is inadequate. In a status report by Dr. Su Tso it was stated that the firm must address:

> The environmental release and pollution controls exercised at the manufacturing facility and other issues as outlined in a telephonic conversation dated 7/23/93 with the firm.

The issues have not been addressed at this time.

REMARKS:

The contract firm which will have responsibility for manufacturing the drug product has not felt that it was their responsibility to validate the certificate of analysis of the drug substance. They do not have impurity standards on hand to perform the analysis for chromatographic purity. The methods for testing drug substance and drug product have been changed in their text and numbering by DPT over that which was provided in the NDA submission. Other comments are found below.

The following is a direct quote, regarding NDA 20-338, from the Form FDA 481(e)-CG, signed by the supervisory inspector of the San Antonio resident post, Mr. John W. Davis, Jr. and issued dated 7/20/93:

"...Present inspection was conducted per inspection request from HFD-324 (Investigations and Compliance Branch), dated 5/21/93, in connection with FDA's review of NDA 20-338, DAL-DO Assignment #930573.

"Significant inspectional observations included: the bulk drug substance supplier's certificate of analysis has not been validated by this firm; THF analysis is not included in this firm's drug substance specifications; the chromatographic purity analysis of the bulk drug substance does not report the amount of each impurity or total amount of impurities; lack of impurity standards; improper calculation of resolution factors; no data to validate the absorptivities of single impurities at 270 nm; failure to evaluate the drug product stability test method to show it is stability indicating; humidity conditions are not controlled or monitored in the stability storage area; dissolution of the active drug substance in the drug product formulation mixing step has not been properly validated; and lack of determination of conditions for completeness and uniformity of solution in the dissolution of Adapalene.

"Samples 93-666-759/797 were collected during this inspection for method validation/verification. The sponsor has been asked to re-submit a methodology package (in triplicate) which reflects the methods in the NDA.

"At the close of the inspection, and FDA-483 was issued to and discussed with management. A written response was promised. A copy of the FDA-483 was sent to the most responsible person, who was not present during the close-out/

"Recommend non-approval of NDA."

CONCLUSIONS & RECOMMENDATIONS:

Recommend nonapproval at the current time. Deficiencies are cited or operations pertaining to review sections are not completed (See review #1); further, the additional comments in the current review are warranted based on the on site inspection of DPT Laboratories, the contract manufacturer of the drug product. The inspection failed to meet requirements to adequately manufacture and control for the processes pertaining to this drug product at DPT Laboratories, San Antonio, TX. **See sections: Raw Materials, Laboratory Controls, Stability, Container/Closure, Environmental Assessment, Manufacturing, and Method Validation.** The subsequent submission of information in response to the FDA-483 has not adequately addressed the items. Comments regarding the submission is contained in the following review in the appropriate sections just cited.

	YES	NO
DRAFT LETTER	x	
TELECONS		x

9-7-93

J. Timper

cc: Org. NDA 20-338
HFD-520/Division File
HFD-520/DeCamp/SUPVCHEM 9/7/93 9/12/93
HFD-520/Timper/CHEM
HFD-520/Bostwick/MO
HFD-520/Browder/PHARM
HFD-520/Sheldon/MICRO
HFD-520/Cook/CSO
HFD-102/CKumkumian [#1 only]
HFC-130/JAllen

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MAR 1 1994

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-338 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 8-Nov-93

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
ORIGINAL	3-19-93	3-26-93	5-5-93
BC	7-1-93	7-2-93	7-6-93
BC	8-12-93	8-16-93	9-30-93
AC	10-29-93	11-1-93	11-8-93

NAME & ADDRESS OF APPLICANT:

Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516
FAX 817 763-5863

CONTACT:

ATTN: Christine E. Shank
Manager, Regulatory Affairs
(817) 551-8516
FAX (817) 763-5863

DRUG PRODUCT NAME

Proprietary: Differin Solution, 0.1%
Established: Adapalene
Code #: CD 271 Topical; AL02866

PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of acne vulgaris

DOSAGE FORM: Topical Solution **STRENGTHS:** 0.1% (1mg/mL)

ROUTE OF ADMINISTRATION: Topical
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Adapalene
CAS-106685-40-9; code names: CD 271; AL02866

Molecular Formula: $C_{28}H_{28}O_3$
Molecular Weight: 412.52
Chemical Name:

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

SUPPORTING DOCUMENTS:

IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Solution (adapalene)

IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Gel (adapalene)

IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Cream (adapalene)

RELATED DOCUMENTS (if applicable):

DMF

DMF

DMF DPT Laboratories Inc.,
San Antonio, TX

DMF

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DMF

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DMF

CONSULTS:

Environmental Assessment: Inadequate

The current status of the Environmental Assessment for the Topical Gel, NDA 20-338 is inadequate. In a status report it was stated that the firm must address:

> The environmental release and pollution controls exercised at the manufacturing facility and other issues as outlined in a telephonic conversation dated 7/23/93 with the firm.

The issues have not been addressed at this time.

REMARKS/COMMENTS:

The review #2, completed 7/6/93, was based on the product specific inspection at DPT Laboratories, San Antonio, Texas; the inspection results was presented to the firm at the time the inspection was completed, 7/2/93, by Mr. Joel Martinez and this reviewer. The FDA 483 cited the failure of that firm, manufacturer of the drug product, to meet satisfactory controls with regard to chemistry and manufacturing. (See below for summary statement quoted from the Form FDA 481(e)-CG, the recommendation for non-approval of NDA.)

The formal recommendation for non-approval, Form FDA 481(e)-CG, signed by the supervisory inspector of the San Antonio resident post, Mr. John W. Davis, Jr., was issued dated 7/20/93.

The response to the FDA 483 was submitted to the file dated 8/12/93, received 8/16/93. This submission was inadequate and addressed in review #3. A sequel to that submission is the subject of this review; the observations of this review will be communicated to the inspector in the San Antonio resident post to address the requirement of the follow-up inspection to address the FDA 483. The proposed drug product, adapalene solution 0.1%, will be manufactured by: DPT Laboratories, Inc., 307 E. Josephine Street, San Antonio, Texas 78215. DPT Laboratories, Inc. currently provides manufacturing, control and distribution services to Owen/Galderma Laboratories, Inc. under contract agreement.

The following is a direct quote, regarding NDA 20-338, from the Form FDA 481(e)-CG, signed by the supervisory inspector of the San Antonio resident post, Mr. John W. Davis, Jr. and issued dated 7/20/93: "...Present inspection was conducted per inspection request from HFD-324 (Investigations and Compliance Branch), dated 5/21/93, in connection with FDA's review of NDA 20-338, DAL-DO Assignment #930573.

"Significant inspectional observations included: the bulk drug substance supplier's certificate of analysis has not been validated by this firm; THF analysis is not included in this firm's drug substance specifications; the chromatographic purity analysis of the bulk drug substance does not report the amount of each impurity or total amount of impurities; lack of impurity standards; improper calculation of resolution factors; no data to validate the absorptivities of single impurities at 270 nm; failure to evaluate the drug product stability test method to show it is stability indicating; humidity conditions are not controlled or monitored in the stability storage area; dissolution of the active drug substance in the drug product formulation mixing step has not been properly validated; and lack of determination of conditions for completeness and uniformity of solution in the dissolution of Adapalene.

"Samples 93-666-759/797 were collected during this inspection for method validation/verification. The sponsor has been asked to re-submit a methodology package (in triplicate) which reflects the methods in the NDA. At the close of the inspection, and FDA-483 was issued to and discussed with management. A written response was promised. A copy of the FDA-483 was sent to the most responsible person, who was not present during the close-out. Recommend non-approval of NDA."

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable.

Specific items which are not approvable are identified under the following headings: Environmental Assessment, Methods Validation, and Establishment Inspections.

JT/ 11-8-93

J. Timper, Review Chemist

cc: Org. NDA 20-338
HFD-520/Division File
HFD-520/DeCamp/SUPVCHEM WD 2/21/94
HFD-520/Timper/CHEM 11/8/93
HFD-520/Bostwick/MO
HFD-520/Osterberg/PHARM
HFD-520/Sheldon/MICRO
HFD-520/Cook/CSO
HFD-102/CKumkumian [#1 only]
HFC-130/JAllen

DIVISION OF TOPICAL DRUGS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-338 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 5-9-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
ORIGINAL	3-19-93	3-26-93	5-5-93
BC	7-1-93	7-2-93	7-6-93
BC	8-12-93	8-16-93	9-30-93
AC	10-29-93	11-1-93	11-8-93
Current review:			
BC	4-1-94	4-5-94	5-9-94
BL	4-4-94	4-5-94	5-9-94
BC	4-26-94	4-28-94	5-9-94

NAME & ADDRESS OF APPLICANT:

Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516
FAX 817 763-5863

CONTACT:

ATTN: Christine E. Shank
Manager, Regulatory Affairs
(817) 551-8516
FAX (817) 763-5863

DRUG PRODUCT NAME

Proprietary: Differin Solution, 0.1%
Established: Adapalene
Code #: CD 271 Topical; AL02866

PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of acne vulgaris

DOSAGE FORM: Topical Solution **STRENGTHS:** 0.1% (1mg/mL)

ROUTE OF ADMINISTRATION: Topical
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Adapalene

CAS-106685-40-9; code names: CD 271; AL02866

Molecular Formula: $C_{28}H_{28}O_3$
Molecular Weight: 412.52
Chemical Name:

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

SUPPORTING DOCUMENTS:

IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Solution (adapalene)
IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Gel (adapalene)
IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Cream (adapalene)

RELATED DOCUMENTS (if applicable):

DMF

DMF

DMF DPT Laboratories Inc.,
San Antonio, TX
DMF

DMF

DMF

DMF

DMF

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DMF

NDA 20-380 Adapalene Topical Gel; line extension of the current NDA 20-338

CONSULTS: REMARKS/COMMENTS:

ACCEPTABLE: The consult regarding the environmental assessment to Dr. Phillip Vincent completed and found acceptable on 12/27/93;

ANSWER TO FDA 483, FOREIGN INSPECTION FAILURE OF FINORGA, IS SUMMARIZED IN THIS REVIEW; VALIDATION AND REVISION of the DMF for the drug substance, is forthcoming and will be reviewed.

METHOD VALIDATION PACKAGES TO ST. LOUIS AND DALLAS FDA LABORATORIES ARE YET TO BE COMPLETED AT THIS TIME.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable.

Specific items which are not approvable are identified under the following headings: Methods Validation and Establishment Inspections.

5/9/94

J. Timper, Review Chemist

cc: Org. NDA 20-338
HFD-540/Division File
HFD-540/DeCamp/SUPVCHEM
HFD-540/Timper/CHEM 5/9/94
HFD-540/Bostwick/MO
HFD-540/Osterberg/PHARM
HFD-540/Sheldon/MICRO
HFD-540/Cook/CSO
HFD-102/CKumkumian [#1 only]
HFC-130/JAllen

7/7/94

DIVISION OF TOPICAL DRUGS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-338 **CHEM.REVIEW #:** 6 **REVIEW DATE:** 5-23-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
ORIGINAL	3-19-93	3-26-93	5-5-93
BC	7-1-93	7-2-93	7-6-93
BC	8-12-93	8-16-93	9-30-93
AC	10-29-93	11-1-93	11-8-93
BC	4-1-94	4-5-94	5-9-94
BL	4-4-94	4-5-94	5-9-94
BC	4-26-94	4-28-94	5-9-94

Method validation completion: 4/29/94; acceptable. Comments to the firm to modify the methods package is attached to this review.

NAME & ADDRESS OF APPLICANT:

Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516
FAX 817 763-5863

CONTACT:

ATTN: Christine E. Shank
Manager, Regulatory Affairs
(817) 551-8516
FAX (817) 763-5863

DRUG PRODUCT NAME

Proprietary: Differin Solution, 0.1%
Established: Adapalene
Code #: CD 271 Topical; AL02866

PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of acne vulgaris

DOSAGE FORM: Topical Solution **STRENGTHS:** 0.1% (1mg/mL)

ROUTE OF ADMINISTRATION: Topical
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Adapalene
CAS-106685-40-9; code names: CD 271; AL02866

Molecular Formula: $C_{28}H_{28}O_3$
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Chemical Name:

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

SUPPORTING DOCUMENTS:

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CD 271 Topical Solution (adapalene)
IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Gel (adapalene)
IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Cream (adapalene)

RELATED DOCUMENTS (if applicable):

DMF

DMF

DMF DPT Laboratories Inc.,
San Antonio, TX
DMF

DMF

DMF

DMF

DMF

DMF

DMF

NDA 20-380 Adapalene Topical Gel; line extension of the current NDA 20-338

CONSULTS: **REMARKS/COMMENTS:** n/a

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable.

Specific items which are not acceptable yet are the Establishment Inspections. Please note comments from the Method Validation evaluation, although determined as acceptable, are requested to be forwarded to the firm at this time.

JTT 5/23/94

J. Timper, Review Chemist

cc: Org. NDA 20-338
HFD-540/Division File
HFD-540/DeCamp/SUPVCHEM WD 5/27/94
HFD-540/Timper/CHEM 5/23/94
HFD-540/Bostwick/MO
HFD-540/Osterberg/PHARM
HFD-540/Sheldon/MICRO
HFD-540/Cook/CSO
HFD-102/CKumkumian [#1 only]
HFC-130/JAllen

WAC 7/7/94

DIVISION OF TOPICAL DRUGS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-338 **CHEM.REVIEW #:** 7 **REVIEW DATE:** 5-31-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
ORIGINAL	3-19-93	3-26-93	5-5-93
BC	7-1-93	7-2-93	7-6-93
BC	8-12-93	8-16-93	9-30-93
AC	10-29-93	11-1-93	11-8-93
BC	4-1-94	4-5-94	5-9-94
BL	4-4-94	4-5-94	5-9-94
BC	4-26-94	4-28-94	5-9-94

Method validation completion was 4/29/94; acceptable. Comments to the firm to modify the methods package was addressed in review #6.

The last document noted in the above list, dated 4-26-94, was reviewed in review #5 and it addressed the response by to the foreign inspection; the **aspects noted in that review are acceptable for an approvable letter with qualifications noted under conclusions/recommendations of this review.**

In addition, the FDA document, from HFD-322, regarding NDAs 20-338/380 (DMF dated 5/19/94 is submitted to the file and summarized in the section Drug Substance in the body of this review. **This document is attached to this review.**

In addition, the FDA document which is the report regarding re-inspection of DPT Laboratories, manufacturer of the drug product, dated 4/15/94, is summarized in the section below Drug Product. **This document is attached to this review.**

In addition, the FDA document which is the letter to from Richard R. Klug, Director, International Technical Operations Branch, regarding the inspection failure of . This letter is dated 5/9/94. This letter is summarized in the section below Drug Substance. **This document is attached to this review.**

NAME & ADDRESS OF APPLICANT:

Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516
FAX 817 763-5863

CONTACT:

ATTN: Christine E. Shank
Manager, Regulatory Affairs
(817) 551-8516
FAX (817) 763-5863

DRUG PRODUCT NAME

Proprietary: Differin Solution, 0.1%
Established: Adapalene
Code #: CD 271 Topical; AL02866

PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of acne vulgaris

DOSAGE FORM: Topical Solution **STRENGTHS:** 0.1% (1mg/mL)

ROUTE OF ADMINISTRATION: Topical **Rx/OTC:** Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Adapalene
CAS-106685-40-9; code names: CD 271; AL02866

Molecular Formula: $C_{28}H_{28}O_3$
Molecular Weight: 412.52
Chemical Name:

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

SUPPORTING DOCUMENTS:

IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Solution (adapalene)
IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Gel (adapalene)
IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Cream (adapalene)

RELATED DOCUMENTS :

DMF

DMF

DMF DPT Laboratories Inc.,
San Antonio, TX
DMF

DMF

DMF

DMF

DMF

DMF

DMF

DMF

NDA 20-380 Adapalene Topical Gel; line extension of the current NDA 20-338

CONSULTS: REMARKS/COMMENTS: n/a

CONCLUSIONS & RECOMMENDATIONS:

The NDA 20-338 is approvable with the following three qualifications:

1. **the effort to identify the impurity be continued (see review to DMF comments to the holder,**

2. **the DMF for drug substance adapalene synthesis, will be updated to include validation of the synthetic process and deficiencies to the inspection are satisfied;**

3. **satisfactory inspection results for sites for manufacturing of the drug product and drug substance.**

JTh 5-31-94

J. Timper, Review Chemist

cc: Org. NDA 20-338
HFD-540/Division File
HFD-540/DeCamp/SUPVCHEM 5/31/94
HFD-540/Timper/CHEM 5/31/94
HFD-540/Bostwick/MO
HFD-540/Osterberg/PHARM
HFD-540/Sheldon/MICRO
HFD-540/Cook/CSO
HFD-102/CKumkumian [#1 only]
HFC-130/JAllen

MC 7/5/94

APR 8 1996

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-338 **CHEM.REVIEW #:** 9 **REVIEW DATE:** 5-18-95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
ORIGINAL	3-19-93	3-26-93	5-5-93
BC	7-1-93	7-2-93	7-6-93
BC	8-12-93	8-16-93	9-30-93
AC	10-29-93	11-1-93	11-8-93
BC	4-1-94	4-5-94	5-9-94
BL	4-4-94	4-5-94	5-9-94
BC	4-26-94	4-28-94	5-9-94
BC	6-15-94	6-16-94	8-25-94
Current review:			
BC	5/1/95	5/3/95	5/18/95

NAME & ADDRESS OF APPLICANT:

Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516
FAX 817 763-5863

CONTACT:

ATTN: Christine E. Shank
Manager, Regulatory Affairs
(817) 551-8516
FAX (817) 763-5863

DRUG PRODUCT NAME

Proprietary: Differin Solution, 0.1%
Established: Adapalene
Code #: CD 271 Topical; AL02866

PHARMACOLOGICAL CATEGORY/INDICATION:
Treatment of acne vulgaris

DOSAGE FORM: Topical Solution; **STRENGTHS:** 0.1% (1mg/mL)

ROUTE OF ADMINISTRATION: Topical; **Rx/OTC:** Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Adapalene

CAS-106685-40-9; code names: CD 271; AL02866

Molecular Formula: $C_{28}H_{28}O_3$

Molecular Weight: 412.52

Chemical Name:

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

SUPPORTING DOCUMENTS:

IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Solution (adapalene)
IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Gel (adapalene)
IND Owen/Galderma Laboratories, Inc.
CD 271 Topical Cream (adapalene)

RELATED DOCUMENTS :

DMF

DMF

DMF DPT Laboratories Inc.,
San Antonio, TX
DMF

DMF

DMF

DMF

DMF

DMF

DMF

NDA 20-380 Adapalene Topical Gel; line extension of the current NDA 20-338

CONSULTS: REMARKS/COMMENTS:

Current update and validation documentation was reviewed in DMF on 5/12/95 and found acceptable. This DMF is the DMF for the drug substance adapalene. The EER was found acceptable on 3/20/95 and an update request is made at the time of this review in the case that time expires on this approval.

CONCLUSIONS & RECOMMENDATIONS:

The NDA 20-338 is acceptable for approval pertaining to chemistry, manufacturing and controls.

JTm 5/18/95

J. Timper, Review Chemist

cc: Org. NDA 20-338
HFD-540/Division File
HFD-540/DeCamp/SUPVCHEM NJ 6/30/95
HFD-540/Timper/CHEM 1/18/95
HFD-540/Bostwick/MO
HFD-540/Osterberg/PHARM
HFD-540/Sheldon/MICRO
HFD-540/~~Cook~~/CSO FORWARD
~~HFD-102/CKumkumian [FI only]~~
HFC-130/JAllen

JBelshad 4/8/96

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation & Research

Date: June 8, 1993

To: Murray M. Lumpkin, M.D.
Director, DAIDP, HFD-520

From: Wilson H. De Camp, Ph.D.
Supervisory Chemist, HFD-520

Subject: NDA 20-338, trade name consult

Please note the attached addendum to Jim's review. I fully agree that this cannot be said to be a "common substance", since it is a new molecular entity.

If the Division decision is to disallow the trade name, it should be on the basis of either of the other objections (i.e., confusion with "dipivefrin" or the implication that the drug is "different").

Wilson H. De Camp, Ph.D.

cc: Orig: NDA 20-338
HFD-102/Kumkumian
HFD-601/Johnson
HFD-520
HFD-520/Rand
HFD-520/Browder
HFD-521/Cook
HFD-520/Sheldon
HFD-520/Timper
init. by SUPVCHEM
wd:6/8/93
n20338.nam

M E M O R A N D U M

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

DATE : 7 June, 1993

TO : Attachment to the Review to the file 20-338

FROM : J. Timper, Review Chemist
Division of Anti-infective Drug Products
HFD-520

SUBJECT : NDA 20-338; Differin (adapalene) Solution, 0.1%; topical drug product, new drug entity

The consult with respect to the name "Differin" was evaluated as unacceptable. The point made in the consult was that "...the drug is a common substance the limitations of which are readily recognized..."

The evaluation was not completely correct due to the fact that this is a 1S product, not marketed in other countries at this time.

Sincerely,

JT 6-7-93

J. Timper, 6/7/93

Consult #221 (HFD-520)

Differin Adapalene Topical Solution 0.1%

A review revealed one name which looks or sounds like the proposed name: Dipivefrin. Dipivefrin is the established name for an anti-glaucoma agent which is available as a 0.1% ophthalmic solution. We believe the similarity in name, strength and dosage form to be of such consequence that the proposed name is misleading as described in 21 CFR 201.10(c)(5).

Furthermore, we find the proposed name puffery in nature since it alludes to the product making a "difference" and having unique effectiveness when in fact the drug is a common substance the limitations of which are readily recognized.

The Committee finds the proposed name unacceptable as described by 21 CFR 201.10(c)(3) and (5).

CDER Labeling and Nomenclature Committee

Ken Johnson, Chair 5-19-93

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Analysis
1114 Market Street, Room 1002
St. Louis, MO 63101
Tel (314) 539-2168
FAX Tel (314) 539-2113

Date: April 29, 1994

From: Henry D. Drew, Ph.D., Chief, Drug Monitoring Branch (HFH-300)

Subject: **Evaluation of NDA - MVP for Adapalene Drug Substance and Differin Topical Solution (NDA: 20-338) submitted by Owen/Galderma Laboratories, Inc., Fort Worth, TX**

To: James M. Timper, Jr., NDE Review Chemist (HFD-520)

The evaluation of the Adapalene drug substance and Differin Topical Solution NDA - MVP has been completed and all methods are acceptable for quality control and regulatory purposes with modification. Please refer to specific comments from the evaluating chemist, Richard E. Kolinski, presented on the attached memorandum and worksheets.

As per program requirements, we are forwarding the original worksheets. We shall retain the reserve sample for 90-days before disposal of remaining sample. If you feel that the reserve sample should be held longer, please contact DDA.

Henry D. Drew

Henry D. Drew, Ph.D.
Chief, Drug Monitoring Branch

file 20-338

Division of Anti-Infective Drug Products (HFD-520)
Microbiology and Drug Control Review Notes #1

NDA # 20-338 **DATE COMPLETED: May 4, 1993**

APPLICANT: Owen/Galderma Laboratories, Inc.
6201 South Freeway
P.O. Box 6600
Fort Worth, Texas 76115

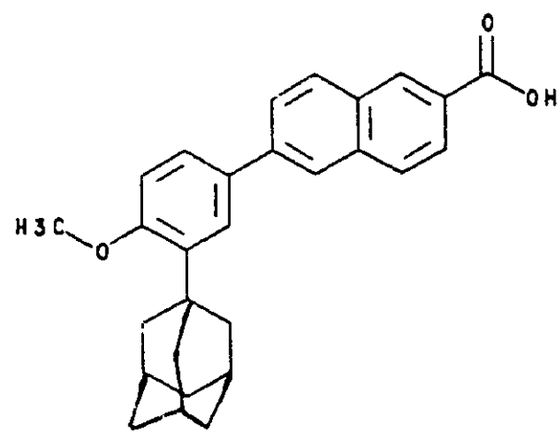
Ms. Christine Shank
Manager, Regulatory Affairs
(817)551-8516

CHEM/THER. TYPE: 1S

SUBMISSION REVIEWED: Original NDA dated March 19, 1993
AMENDMENT DATED: April 29, 1993
PROVIDING FOR: Microbial Limit Assay procedure

PRODUCT NAMES(S):
Proprietary: DIFFERIN
Non-Proprietary/USAN: adapalene
Chemical: 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

STRUCTURAL FORMULA:



Empirical Formula $C_{28}H_{28}O_3$
MOL. WT. = 412.52

DOSAGE FORM and STRENGTHS: 0.1% Sterile ophthalmic solution

ROUTE OF ADMINISTRATION: Topical

PHARMACOLOGICAL CATEGORY: Retinoid

RELATED DOCUMENTS: IND adapalene topical solution; IND adapalene topical gel; IND adapalene topical cream.

INITIAL SUBMISSION:
Received by CDER: March 26, 1993
Received by Reviewer: April 14, 1993
Review Completed: May 4, 1993

AMENDMENT: Dated April 29, 1993

REMARKS: This drug is not an anti-infective product, therefore, there is no microbiology section. Most of the sections in our normal microbiology review are, therefore, not applicable.

CONCLUSIONS:
FROM THE MICROBIOLOGY AND MICROBIOLOGICAL CONTROLS VIEWPOINTS THIS PRODUCT IS APPROVABLE. THE APPLICANT SHOULD, HOWEVER, SUBMIT DATA TO SHOW THAT PREPARATORY TESTING HAS BEEN PERFORMED TO SHOW THE VALIDITY OF THE MICROBIAL LIMITS TESTS DONE ON THE PRODUCT. THIS TESTING IS DESCRIBED IN THE USP MICROBIAL LIMITS TESTS <61>.

Peter A. Dionne
Peter A. Dionne
Microbiologist, HFD-520

cc: Orig. NDA # 20-338
HFD-502
HFD-520
HFD-520/Micro/Dionne
HFD-520/MO/Boswick
HFD-520/Chem/Timper
HFD-520/CSO/Cook

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/SMicro/ASheldon
B 4/26/93, 5/5/93
5/4/93

M E M O R A N D U M

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

DATE : 8 December, 1993

TO : Owen/Galderma Laboratories, Inc.
ATTN: Christine E. Shank
Manager, Regulatory Affairs
Post Office Box 6600
Fort Worth, Texas 76115
(817) 551-8516

FROM : James Timper, Chemist,
Division of Anti-infective Drug Products
HFD-520; 301-44-6714, (FAX 443-5803)

SUBJECT : 1.) Environmental assessment
2.) Related substance standards for Adapalene

I want to inquire if you can provide any information on the above two items that pertain to NDA 20-338, Differin (adapalene) Solution, 0.1%.

Have the related substances been obtained from the manufacturer of the drug substance on an FDA inspection or should the related substances be acquired now at DPT Laboratory, San Antonio, that were not available for the inspector at the DPT Laboratory during that product specific inspection? At this time I am asking for this information from the foreign inspection branch of FDA and hopefully this problem will be quickly resolved.

Also, I've included the environmental assessment comments requested by Dr. Tso. Have these been addressed at this point?

Adapalene for use in commercial product production is manufactured by

DMF The facilities and organization of are described in the DMF

Sincerely,

J Timper 12-8-93

James Timper

CC: RCook

U

M E M O R A N D U M

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

Division of Drug Analysis
St. Louis, MO 63101
Tel FTS (314) 539-2011
FAX Tel FTS (314) 539-2113

DATE : April 28, 1994

FROM : Richard E. Kolinski, Chemist
Drug Monitoring Branch (HFH-300)

SUBJECT: NDA 20-338, ADAPALENE BULK and DIFFERIN (Adapalene) TOPICAL SOLUTION, 0.1% (w/v)

TO : J. Timper, Review Chemist
Division of Anti-infective Drug Products (HFD-520)

THROUGH: Harry D. Coffman, Supervisor, Laboratory A
Division of Drug Analysis (HFH-300)

The bulk drug substance, Adapalene, meets the specifications described in this NDA-MVP. The bulk drug appears to be a pure substance.

The drug dosage form, Adapalene Topical Solution 0.1%, meets the specifications described in this NDA-MVP.

The following comments refer to both NDA-MVP volumes. Item 4a is Volume 1 and Item 4b is Volume 2. The applicant is Galderma Laboratories (Fort Worth, TX). The bulk drug manufacturer is The topical solution manufacturer is DPT Laboratories (San Antonio, TX).

After review of the following comments and the corrections indicated, the methods evaluated should be suitable for quality control and regulatory purposes.

cc: JT (Review Chemist)
DDA
HDC
REK

Memorandum of a Telephone Conversation

Date: July 23, 1993

NDA: 20-338

Between: Christine Shank
Regulatory Affair Manager
Owen Galderma
(817) 263-2676
Fax (817) 263-2667

And: Su C. Tso, Ph.D.
HFD 520
(301) 443-4300
fax (301) 443-5803

Subject: **Additional Information on Environmental Assessment**

I called Christine Shank to provide me with the following information on environmental assessment.

1. Toxicity data or LD_{50} of LC_{50} for the bulk drug substance adapalene

2. MSDS sheet for adapalene

3. Draft label (package insert) for the drug product DIFFERIN

4. Estimation of environmental release based production volume and control exercised should be provided. Describe how and where the wastes stream are disposed of. List environmental permits (Air, wastewater, and solid wastes) for the production of finished dosage form at the domestic manufacturing facility.

5. For foreign manufacture, provide a Certificate of Environmental Compliance from the foreign government authority (with specificity to the manufacturing of drug substance and/or drug product).

I suggested to her a revised EA with all the above information included should be submitted. The EA should not contain confidential information. All confidential information should be submitted as appendix.

I promised the firm that I would fax my telephone requests to her on Monday.

Call me if you have any question.

M E M O R A N D U M

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

DATE: ~~May~~ July 28, 1993

FROM: Phillip Vincent, Ph. D.
Environmental Assessment Officer HFD-102

Su C. Tso, Ph. D.
Environmental Staff

SUBJECT: Environmental Concerns-- NDA 20-338,
Differin (appalene) Topical Solution, 0.1%

TO: R. Cook, HFD-520

Owen Galderma

The environmental assessment for DIFFERIN has been carefully reviewed. Please transmit the following to the firm and copy HFD 102:

The Center has made a preliminary review of your environmental assessment for NDA 20-338, Differin (appalene) Topical Solution, 0.1% and notes several deficiencies which require your attention.

It is a common and incorrect assumption that, because a product or part of a product is located in a foreign country, no environmental review of that aspect of the application is required. Under NEPA, Executive Order 12114 "Environmental Effects Abroad of Major Federal Actions", and 21 CFR 25.50, the requirement for evaluation of the impact of agency actions on the global commons and on foreign countries is established.

The preferred method for addressing item 6 of the EA format is to provide the information requested, substituting the requirements of the foreign country where the manufacturing will occur for Federal, State and local emissions requirements. Sometimes applicants have found that it is more convenient to obtain a letter or letters from the appropriate offices(s) of the foreign government stating that the manufacture of the product(s) that is the subject of the application has been evaluated by that government and that it meets their requirements for emissions and occupational controls. Provided that the letter(s) has some specificity about the drug product that would be manufactured under the NDA and the governments's requirements, such a letter can be used in lieu of the information requested in section 6 of the EA format.

For your application, it is governed by 21 CFR 25.31a(b)(3). The approval of NDA's for human drugs and approval of licenses for biological products, when the drugs or biological products are intended for the prevention, treatment, or diagnosis of a rare disease or for a similarly infrequent use; for ophthalmic or topical application; or for local or general anesthesia; the following information is required for the items specified:

(i) **Format item 6. For the site(s) of production: list the substances expected to be emitted; state the controls exercised; include a citation of, and statement of compliance with, applicable emissions requirements (including occupational) at the Federal, State, and local level; and discuss the effect the approval will have upon compliance with current emissions requirements at the production site(s). Estimate the maximum yearly market volume of the drug product to aid in determining whether approval of the application could result in potentially significant environmental introductions from use of the product.**

If the manufacturing facility is located in a foreign country, you might submit **a Certificate of Environmental Compliance from the foreign government authority (with specificity to the manufacturing of drug substance and/or drug product)** in lieu of the information required in item 6 of the EA format.

Please resubmit a complete Environmental Assessment to support your application. The EA should be a single document from the applicant for review by the Environmental Assessment Officer. The document should not be annotated "confidential" or with other proprietary statement. All confidential information/data should be provided in the Appendix.

CC: Original NDA 20-338, Document Room HFD-520
EA File 20-338
Reviewer file HFD-520/Tso
HFD-520/WHDeCamp
Reader File HFD-102/Vincent
Supervisory CSO HFD-520/Cook

NDA 20-338

Christine Shank
Manager, Regulatory Affairs
Galderma Laboratories, Inc.
Suite 300
3000 Alta Mesa Blvd.
P.O. Box 331329
Fort Worth, TX 76163

FEB 24 1994

Dear Ms. Shank:

We acknowledge receipt on January 11 and February 1, 1994, of your amendments dated January 10 and 31, 1994 respectively, to your new drug application (NDA) for adapalene topical solution, 0.1%.

We consider these submission to be major amendments received by the Agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new user fee due date is **June 24, 1994.**

Should you have any questions concerning this application, please contact Ms. Maria Rossana R. Cook, Project Manager, at 301-443-0257.

Sincerely yours,

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 20-338
HFD-520
HFD-520/ACTG DIV DIR/Gavrilovich
HFD-520/MO/Bostwick MB 2.24.94
HFD-520/PHARM/Mainigi
HFD-520/PHARM SUPV/Osterberg
HFD-520/CHEM/Timper
HFD-520/MICRO/Dionne
HFD-520/MICRO SUPV/Sheldon
HFD-426/BIOPHARM/Dorantes
HFD-426/BIOPHARM SUPV/Pelsor
HFD-713/STAT/Chakravarty
HFD-713/STAT SUPV/Harkins
HFD-521/PROJ MGR/Cook 2/24/94
REVIEW EXTENSION

Concurrences:

HFD-520/MO SUPV/Chambers MMC 2/24/94
HFD-520/CHEM SUPV/De Camp

EA

&

FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Differin
(adapalene topical solution)

0.1%

NDA 20-338

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-338

Galderma Laboratories, Inc. has submitted an environmental assessment to support a new drug application dated March 19, 1993 . The application was submitted in pursuant to section 505 of the Food, Drug, and Cosmetic Act for DIFFERIN (adapalene), 0.1% Solution.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered all the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their application, the firm has prepared a environmental assessment according to 25.31a(b)(3) which evaluates the environmental impacts of the manufacture and use of the drug products. The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the finished products are expected to minimize occupational exposures and environmental release. The amount of residues of the drug substance and its major metabolites entering the environment as a result of administering the drug to humans are insignificant, they will have negligible impact in the environment.

Su C. Tso — 12/27/93

Prepared by Su C. Tso, Ph.D.
Environmental staff

Date

P G Vincent — 1-3-94 PGV

Phillip G. Vincent, Ph.D
Environmental Assessment Officer

Date

Charles Kumkumian — 1/10/94

Charles S. Kumkumian, Ph.D
Assistant Director of Chemistry

Date

cc: Original: NDA 20-338
HFD-520/SCTso
HFD-520/Cook
HFD-520/JTimper
HFD-102/PVincent
FONSI file: NDA 20-338

ORIGINAL

March 19, 1993

6201 South Freeway
P.O. Box 6600
Fort Worth, Texas 76115
(817) 293-0450

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
ATTENTION: Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

RE: NDA 20-338
DIFFERIN™ SOLUTION, 0.1%
(Adapalene Topical Solution)
Original Application Submission

Dear Sir or Madam:

The applicant, Owen/Galderma Laboratories, Inc., is pleased to submit herewith a New Drug Application for DIFFERIN™ SOLUTION, 0.1%. This application is submitted pursuant to Section 505 (b) of the Federal Food, Drug, and Cosmetic Act and in accordance with the procedures and requirements established in Part 314 of Title 21 of the *Code of Federal Regulations*.

The proposed new drug product is a topical solution dosage form of the new chemical entity, adapalene (*USAN*), indicated for the treatment of acne vulgaris. The drug product has been the subject of clinical investigations in the United States under IND since 1988. The approved product will be made available to patients only by prescription from a licensed physician.

Pre-NDA Submission
On December 14, 1992 the applicant submitted the Chemistry, Manufacturing and Controls Data section of this New Drug Application pursuant to the provisions of 21CFR 314.50(d)(1)(iv). Accordingly, this submission of the remaining sections of the application completes the requirements for a full application. The full application index in volume 2.1 identifies the information provided in the presubmission. A copy of the December 14, 1992 presubmission letter is attached for reference.

Organizational Relationships and Affiliations
For clarification of the relationships of the companies involved with the development of the drug, we offer the following brief explanation. Owen/Galderma Laboratories, Inc., Fort Worth, Texas, the sponsor of this application, and , the developer of the drug substance, are organizations existing under the joint ownership of Nestlé S.A. and L'Oréal. Owen/Galderma Laboratories, Inc. and Alcon Laboratories, Inc. are affiliate companies through the ownership interest of Nestlé S.A. (Alcon is a wholly owned

subsidiary of Nestlé). DPT Laboratories, Inc., San Antonio, Texas (formerly known as Dermatological Products of Texas, Inc.) is independently owned and operated by Dorman-Feik Acquisitions Corp. Owen/Galderma contracts with DPT Laboratories, Inc. for the production, control and distribution of finished (marketed) drug products and for production and control of drug products under investigational development. The collaborative participation by these companies in the conduct of preclinical and clinical studies and in drug and formulation development is reflected in this application.

Drug Development Overview

Drug development and preclinical studies were conducted or sponsored by Galderma, Valbonne, France. Initial safety and efficacy testing (phase 1 and 2 studies) in human volunteers and acne patients was also conducted by Galderma in Europe. Subsequent phase 2 and 3 clinical investigations have been conducted both in the United States under IND and in Europe. In addition to the topical solution dosage form described in this application, the drug is being investigated in aqueous gel and cream dosage forms under INDs respectively. The reviewers will note that supportive, comparative and primary studies (preclinical and clinical) employing in particular the aqueous gel dosage form are included in this submission. A separate and complete New Drug Application for DIFFERIN™ Gel, 0.1% is currently being assembled for filing which will contribute materially to the overall efficacy profile of the drug and corroborate the safety of its intended use.

Dosage Form

The dosage form described in this application is an alcohol base formulation containing the drug substance, adapalene, in solution. Reviewers are advised that in all instances where reference is made to a "lotion" dosage form, the term "lotion" is the European expression used to describe the solution dosage form. In preparing this document for U.S filing, overall summaries and discussions make reference to the drug product as a solution as defined in the *United States Pharmacopeia*. Original reports, however, retain the "lotion" expression.

FDA Meetings and Correspondence

The meetings and correspondence with the Food and Drug Administration which significantly influenced the development of this application are briefly described as follows:

- On September 19, 1989, Dr. Browder, Mr. Davitt and Dr. Osterberg of FDA met with sponsor representatives to discuss the nonclinical studies planned for submission in support of an NDA. A satisfactory agreement was reached by the participants on the list of required pharmacology and toxicology studies with the exception of the conduct of a study to assess photocarcinogenicity potential. The sponsor expressed several reasons why a photocarcinogenicity study should not be a requirement for formulated adapalene (CD 271) and in follow-up correspondence of October 27, 1989 agreed to labeling precautions as a means of addressing the matter. In a letter from Dr. Murray Lumpkin dated April 27, 1990, the agency concurred that the sponsor must provide precautionary labeling clearly stating that there have been positive findings relating to photocarcinogenicity for retinoids and related compounds. If the sponsor did not,

however, elect to do precautionary labeling, then studies would be required. Preparatory to the submission of this NDA, the sponsor, in a letter dated December 3, 1991, reaffirmed the commitment to include a statement in the labeling. The reviewer will find that the PRECAUTIONS section of the draft labeling for the drug product contains wording which closely follows the statement suggested in Dr. Lumpkin's April 27, 1990 letter.

- The second meeting was a Pre-NDA meeting that took place on November 7, 1990 which included Drs. Lumpkin, Burlington, Evans, Rand, Harkins and Ms. Cook of FDA and sponsor representatives. The focus of this meeting was to review the available clinical data from both U.S. and European studies and to assess the completeness of the clinical evidence of safety and efficacy towards making a determination of fileability of an NDA for the drug product. Based on several comments and concerns expressed by agency participants with regard to the one completed vehicle-controlled study, the sponsor elected to conduct an additional vehicle-controlled study (No. 9104-CD271L-EV) which was initiated in March, 1991 and completed in August, 1991. The submission of this application is based on the November 7, 1990 meeting discussions and the completion of the subsequent clinical study.

- October 19, 1992 correspondence to IND addressed the matter of submitting "line listings" for patients enrolled in pivotal clinical studies. The format of the computer generated listings provided in this application closely follow the recommendations and suggestions made by agency personnel.

Contact Person

Due to diverse location of key scientific and technical personnel within the organizations responsible for the contents of this application, it is requested that any questions or comments regarding this submission should be directed to the person named as follows:

Ms. Christine Shank (Mail Code OP)
Manager, Regulatory Affairs
Owen/Galderma Laboratories, Inc.
P.O. Box 6600
Fort Worth, Texas 76115

Telephone: (817)551-8516
Fax: (817)763-5863

Contents of the Application

The New Drug Application for DIFFERIN™ SOLUTION, 0.1% consists of the following:

PRE-NDA SUBMISSION OF CHEMISTRY, MANUFACTURING, AND CONTROLS DATA VOLUMES 1.1 - 1.3 - Submitted December 14, 1992.

FULL NEW DRUG APPLICATION - VOLUMES 2.1 - 2.68 - Submitted March 19, 1993.

VOLUME 2.1

Cover Letter
Form 356h and Letters of Authorization
Generic Drug Enforcement Act Certification
Applicable Patents (ITEM 13)
Reviewer's Guide to the Application
ITEM 1. APPLICATION INDEX
ITEM 2. SUMMARY
ITEM 4.c. LABELING

VOLUMES 2.2 - 2.42

ITEM 5. NONCLINICAL PHARMACOLOGY and TOXICOLOGY SECTION

VOLUMES 2.43 - 2.44

ITEM 6. HUMAN PHARMACOKINETICS and BIOAVAILABILITY SECTION

VOLUMES 2.45 - 2.61

ITEM 8. CLINICAL AND STATISTICAL DATA SECTION

VOLUMES 2.62 -2.66

ITEM 11. CASE REPORT TABULATIONS

VOLUMES 2.67 - 2.68

ITEM 12. CASE REPORT FORMS

The applicant extends its sincere appreciation to the agency staff and reviewers for their time spent in review and consideration of this application. We will be delighted to assist if there are any questions.

Sincere regards,

Christine Shank

Christine E. Shank

DESK COPY VOLUME 2.1: Ms. Rosemary Cook
Division of Anti-Infective Drug Products
HFD-520, Room 12B-05

cc: Mr. Stephen W. Clark
President, OWEN/GALDERMA Laboratories, Inc.

CES/letter
CES/sam

APPLICANT COMMENTS AND REASONS
FOR ADDITIONAL CHANGES IN LABELING

CLINICAL PHARMACOLOGY

Clinical studies with Adapalene Solution and Gel 0.1% provide evidence of its activity in reducing both inflammatory and noninflammatory acne lesions. Additionally, animal and *in vitro* assays have also demonstrated the anti-inflammatory activity of adapalene.

The proposed text in this section of the labeling can be verified in the Summary Section of the applications:

NDA 20-338
Volume 2.1 pages 2 0018 - 2 0029
pages 2 0067 - 2 0070
pages 2 0271 - 2 0276

NDA 20-380
Volume 1.1 pages 2 0017 - 2 0027
pages 2 0077 - 2 0079
pages 2 0292 - 2 0297

Pharmacokinetics

Quantifiable levels (limit of quantification = ng/mL) of adapalene have not been found in the plasma of acne patients in clinical trials. Only trace amounts of adapalene were detected (detection limits = ng/mL) in plasma of a few of the acne patients prescribed adapalene gel 0.1%. Thus the modified text accurately reflects the findings <u>for</u> <u>both</u> the solution and gel dosage forms.

Reference is made to the Summary Section of the applications:

NDA 20-338
Volume 2.1 pages 2 0208 - 2 0214

NDA 20-380
Volume 1.1 pages 2 0212 - 2 0218

CONTRAINDICATIONS

Although there was no evidence of contact allergic reactions to adapalene solution or gel during the safety or efficacy studies, the applicant acknowledges that the proposed statement is reasonable for a topical drug product as certain individuals can be hypersensitive to vehicle components. The proposed statement, however, clearly does not warrant a WARNING classification.

Reference is made to the Summary Section of the applications:

NDA 20-338
Volume 2.1 pages 2 0278 - 2 0292

NDA 20-380
Volume 1.1 pages 2 0297 - 2 0308

PRECAUTIONS: ***General*:**

The second sentence of the first paragraph has been abbreviated because while we agree with the advice to minimize exposure to sunlight and etc. there is no evidence that patients with sunburn will be more susceptible to sunlight as a result of using the drug.

Reference is made to the Summary Section of the applications:

NDA 20-338
Volume 2.1 pages 2 0235 - 2 0237
pages 2 0278 - 2 0292

NDA 20-380
Volume 1.1 pages 2 0246 - 2 0248
pages 2 0297 - 2 0308

The second paragraph has been expanded to caution patients against application of the product to cuts, abrasions or eczematous skin which is consistent with our earlier proposal as well as labeled cautions for other topical retinoids.

Drug Interactions:

The applicant re-proposes to add the information from the adapalene study with other concurrent acne therapies (last sentence of the section). We believe this is useful information for the prescribing physician.

Reference is made to the Summary Section of the application:

NDA 20-338
Volume 2.1 pages 2 0237 - 2 0238

***Carcinogenesis, Mutagenesis, Impairment of Fertility*:**

We have modified the section placing related statements in proper sequence. The chemical and photochemical stability characteristics of adapalene are cited as relevant since it is known that other marketed topical retinoids are very labile molecules in the presence of oxygen and light.

Reference is made to the Summary Section of the applications:

NDA 20-338
Volume 2.1 pages 2 0035 - 2 0037
page 2 0126
page 2 0223
pages 2 0235 - 2 0237

NDA 20-380
Volume 1.1 pages 2 0031 - 2 0033
page 2 0131
page 2 0234
pages 2 0246 - 2 0248

Pregnancy:

The applicant has re-proposed Pregnancy Category C labeling as appropriate for topical administration of this drug. This is consistent with the current labeling for topical retinoids and for other topical drugs such as corticosteroids. Reference is made to the findings from the reproduction studies with adapalene for verification of the description of the animal studies. Dosages have been correlated to adult human daily topical application for both *Oral* and *Topical* routes.

NDA 20-338
Volume 2.1 pages 2 0130 - 2 0149

NDA 20-380
Volume 1.1 pages 2 0136 - 2 0152

ADVERSE REACTIONS:

The recommended model for presentation of adverse reactions has been adopted for both the solution and gel. The incidence of events includes "related" and "possibly related" effects from the medical events tables in the Summary Section of the applications.

NDA 20-338
Volume 2.1 page 2 0303

NDA 20-380
Volume 1.1 page 2 0238

DOSAGE AND ADMINISTRATION:

The applicant proposed to state, in the second paragraph, that "Therapeutic results should be noticed after two weeks with definite beneficial effects evident after four weeks". A table summarizing the clinical improvement parameters (total lesions, inflammatory lesions and noninflammatory lesions) from clinical studies with the solution and gel is attached for verification of the accuracy of the statement.

Adapalene Gel - Review of Clinical Improvement (Onset)									
	Percent Change Total Lesions			Percent Change Noninflammatory Lesions			Percent Change Inflammatory Lesions		
Study	Wk 2	Wk 4	Wk 8	Wk 2	Wk 4	Wk 8	Wk 2	Wk 4	Wk 8
C-89-61	-22*	-23*	-34*	-22*	-18*	-33*	-21*	-33*	-35*
9105	-6*	-11*	-17*	-5*	-10*	-16*	-9*	-15*	-23*
CR 88051 (p-value not reported)	-36	-45	-62	-42	-51	-64	-18	-27	-43
CR 89064 (p-value not reported)	-22	-37	-51	-23	-39	-55	-16	-30	-40
C-89-32	-17*	-31*	-38*	-16*	-29*	-35*	-10*	-26*	-39*

* $p < 0.05$ within treatment changes from baseline

Adapalene Solution - Review of Clinical Improvement (Onset)									
	Percent Change Total Lesions			Percent Change Noninflammatory Lesions			Percent Change Inflammatory Lesions		
Study	Wk 2	Wk 4	Wk 8	Wk 2	Wk 4	Wk 8	Wk 2	Wk 4	Wk 8
PC 86030 (p-value not reported)	-28	-39	-59	-30	-44	-66	-20	-22	-35
C-88-27 (p-value not reported)	-9	-12	-23	-4	-18	-22	-14	-18	-27
9104	-18*	-24*	-37*	-20*	-25*	-37*	-10*	-23*	-36*
PH 87027 (p-value not reported)	-23	-36	-51	-35	-44	-51	+8	-7	-43
C-88-26** (p-value not reported)	-20	-28	-47	-24	-30	-51	-13	-25	-38
CR 88043 (p-value not reported)	-31	-44	-58	-33	-45	-59	-23	-39	-53

* $p < 0.05$ within treatment changes from baseline

** estimated according to graph

Co. Corres

GALDERMA

DUPLICATE

BL

June 3, 1994

Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
DRAFT LABELING - Revised May 1994

NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%
DRAFT LABELING - Revised May 1994

Dear Sir or Madam:

Reference is made to the "Draft" physician insert labeling for Adapalene Topical Gel, 0.1% (NDA 20-380) provided to us via FAX on 5/20/94. As we were advised by Ms. Rosemary Cook to use this draft as a model for the solution dosage form covered under NDA 20-338, we are enclosing our re-drafts of labeling for both dosage forms with this submission. Reviewers will note that the text we propose is the same for both products except as differences in dosage form dictate in the sections for DESCRIPTION, ADVERSE REACTIONS and HOW SUPPLIED.

Since the 5/20/94 FDA draft was based only on recommendations from the medical/clinical review of NDA 20-380 and the biopharmaceutic and pharmacology reviews have not been considered, we have basically retained our original proposals for the sections relating to these other reviews. We have however adopted many of the review recommendations for the PRECAUTIONS section which suggest labeling for topical retinoids as a class. Also, where specific animal and/or human studies have demonstrated differences in the action or activity of the drug from other topical retinoids, the text has been modified to accurately reflect the differences.

Our most notable exception to the draft regards the recommendation for Pregnancy Category X. We have re-drafted this section to again propose Category C Labeling and have accurately represented the findings from the relevant animal studies. Based on the available data, we submit that our proposed labeling clearly meets the criteria for Pregnancy Category C Labeling.

GALDERMA LABORATORIES, INC.

SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

On the following pages are the applicant's comments and reasons for revisions which differ from the FDA draft recommendations. Please note that references, as applicable, are made to information in the Summary Sections of the applications in support of and documentation for the proposed revisions.

An Archival Copy is provided for each application. Review Copies are also enclosed for each review discipline.

We appreciate the agency's consideration of these amendments.

Sincere regards,

Christine Shank

Christine Shank
Manager Regulatory Affairs

Archival Copy
Review Copies (5)

DESK COPY: Ms. Rosemary Cook
(diskette included)

GALDERMA

PATENT INFORMATION AMENDMENT - July 6, 1995

NDA 20-338
DIFFERIN™ (adapalene) Topical Solution, 0.1%

21CFR 314.53 Submission of Patent Information
(*Federal Register*, October 3, 1994)

The applicant, Galderma Laboratories, Inc., submits the following information for each patent that claims the drug substance, adapalene, and that claims a method of use of the drug as described in paragraph (b) of section 314.53. This submission amends the information provided in the original application to reflect extended patent terms under the Uruguay Round Agreements Act of December 8, 1994.

Pursuant to section 314.53 (c) (1) the applicant submits:

(i) U.S. Patent No. 4,717,720
Patent Expiration Date: April 10, 2006

(ii) Type of Patent: U.S. Patent No. 4,717,720
claims the compound 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid, ADAPALENE, and its use in effective amounts in pharmaceutical compositions suitable for topical administration.

(iii) Name of Patent Owner:

(iv) The U.S. agent for the patent owner is:

The applicant, Galderma Laboratories, Inc., is a legal corporate entity doing business in the U.S. at 3000 Alta Mesa Blvd., Fort Worth, Texas 76133.

Pursuant to section 314.53 (c) (2) (i) the applicant Galderma Laboratories, Inc. submits the following declaration:

The undersigned declares that Patent No. 4,717,720 covers the formulation, composition, and/or method of use of DIFFERIN™ (adapalene) Topical Solution, 0.1%. This product is the subject of this application for which approval is being sought.

Christine Shank
Christine E. Shank
Manager, Regulatory Affairs
Galderma Laboratories, Inc.

July 6, 1995
Date

GALDERMA

DUPLICATE

NDA AMENDMENT

August 27, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 30 1993
HFD-520

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
4-Month Safety Update

Dear Sir or Madam:

Please find enclosed the 4-Month Safety Update to NDA 20-338 submitted pursuant to 21 CFR 314.50 (d) (5) (vi) (*b*). The report is comprehensive for all dosage forms of adapalene and includes information from all U.S. and foreign studies.

If there are any questions please contact me at (817)263-2676

Sincere regards,

Christine Shank

Christine Shank

Enclosures: Archival Copy
Clinical Review Copy
Extra Copy

DESK COPY: Ms. Rosemary Cook
HFD 520, Room 12B-05

CES/sam

GALDERMA LABORATORIES, INC.

SUITE 300 3000 ALTA MESA BLVD. P.O. BOX 331329 FORT WORTH, TX 76163 (817) 263-2600

GALDERMA

trip

DRUG AMENDMENT
SU

February 28, 1994

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Safety Update

Dear Sir or Madam:

Pursuant to a recent request from Ms. Rosemary Cook, FDA Project Manager, please find enclosed a Safety Update report. This report is comprehensive for all dosage forms of adapalene and includes information from all U.S. and foreign studies. Information is also provided on the status of worldwide marketing applications. To date the drug, adapalene, in any dosage form has not been commercially distributed in any country.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817)263-2676

Enclosure: Archival Copy
Clinical Review Copy
Extra Copy

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

GALDERMA

September 2, 1994

Mr. Jim Timper
FDA/CDER
Division of Topical Drug Products (HFD-540)
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
Adapalene Topical Solution, 0.1%
Methods Validation Package

Dear Mr. Timper:

Reference is made to our telephone conversation on September 1, 1994 regarding methods validation for Adapalene drug substance, Adapalene Topical Solution and Adapalene Topical Gel to be conducted by the

As agreed, I contacted We were able to establish that Mr. Hanus has a copy of the current Methods Validation Package for Adapalene Gel (June 16, 1994 Amendment to NDA 20-380), but does not have a current package for Adapalene Solution.

In order to accommodate Mr. Hanus' immediate needs and for ease of reference, I have compiled a Methods Validation Package for Adapalene Solution from the past amendments to NDA 20-338. For reference please note as follows the amendments relative to the methods revisions:

Test	Procedure	Amendment Date
Appearance/Clarity, Color and Odor	80.1931.2SMA.4009	11/24/93
TLC ID Test for Adapalene	73.4545.00	11/24/93
ID and HPLC Assay for Adapalene	73.4553.01	6/15/94
Alcohol ID Test A	73.4539.00	11/24/93

GALDERMA LABORATORIES, INC.
SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

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Test	Procedure	Amendment Date
Alcohol ID and Assay by GC	73.4552.00	11/24/93

As regards the tests, specifications and methods for Adapalene Drug Substance, they are identical whether for material used in production of Adapalene Topical Solution or Adapalene Topical Gel. A statement to this effect is provided in the Drug Substance section of the Methods Validation Package being provided to Mr. Hanus and enclosed herewith.

For the sake of consistency and completeness I am submitting identical packages to the NDA and the

Please contact me if you have any questions.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone (817)263-2676
FAX (817)263-2667

COPY: Mr. Jim Hanus
Dallas District Office
3032 Bryan Street
Dallas, Texas 75204

April 29, 1993

Owen/GALDERMA
6201 South Freeway
P.O. Box 6600
Fort Worth, Texas 76115
(817) 293-0450

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
DIFFERIN Solution, 0.1%
(Adapalene Topical Solution)
Response to Special Request

Dear Sir or Madam:

Reference is made to a request by telephone on April 26, 1993 from Mr. Peter Dionne, FDA Microbiologist.

Please find enclosed the following information in response to Mr. Dionne's request:

- Microbial Limit Assay - Procedure No.: 80.1933.2MLA.1001

  The enclosed procedure is the method which the drug product manufacturer, DPT Laboratories, Inc., uses to determine microbiological quality of finished products. This procedure was used for testing the eight (8) stability lots from the validation batches produced at DPT Laboratories, Inc.. This procedure conforms with USP test requirements and will be used for routine finished product release testing of DIFFERIN Solution, 0.1%.

- Microbiology Laboratory Reports - the enclosed reports provide actual results from the initial Microbial Limit Assay tests preformed on the eight (8) stability lots from the validation batches produced at DPT Laboratories, Inc.. Please note on each report there are references which correspond to sections 3.2.2 and 3.2.3 of procedure no. 80.1933.2MLA.1001. These sections describe how the samples were prepared prior to testing.

  Validation Batches - initial laboratory reports

FBGF	FBGF-1	10mL
	FBGF-2	30mL
	FBGF-3	60mL
FBGG	FBGG-1	10mL
	FBGG-2	30mL
	FBGG-3	60mL
FBGH	FBGH-1	10mL
	FBGH-3	60mL

We sincerely hope you find the information satisfactory. Please let us know if you have any further questions in this regard.

Sincerely,

Christine E. Shank
Manager, Regulatory Affairs

Desk Copy: Mr. Peter Dionne
HFD-520, Room 12B-17

Ms. Rosemary Cook
HFD-520, Room 12B-05

CES/pc
Enclosures

GALDERMA

DUPLICATE

ORIG

BZ

May 6, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
DIFFERIN Solution, 0.1%
(Adapalene Topical Solution)
Response to Special Request

Dear Sir or Madam:

Reference is made to a telephone call from Ms. Rosemary Cook, FDA Project Coordinator, on Friday, April 30, 1993. Ms. Cook discussed with me a list of administrative items needed to complete the initial application filing review process.

Please find, as follows, our understanding of the issues and our response to each:

1. "Provide a statement that the Integrated Summary of Safety includes all data from U.S. (domestic) sources/studies. Include a statement to the effect that there are no additional data to report from foreign sources, as the drug product is not currently marketed in any country outside the U.S.. Advise as to the status of U.S. studies and the closing date for preparation of the integrated summary."

   The applicant submits, herewith, a signed statement regarding status of studies and reports of all safety data for Adapalene Solution both from foreign and domestic sources. In effect, the "closing date" for preparation of the Integrated Summary of Safety was June 1992 following finalization of the report for the last U.S. Clinical Study (9104-CD271L-EV). ATTACHMENT A

2. "Provide a list of all manufacturing facilities and include the site address. Identify the function of each facility and advise as to inspection readiness."

Please find enclosed the requested facilities information and a statement of inspection readiness. ATTACHMENT B
This information also responds, in full, to Mr. Timper's request dated April 20, 1993 (received via FAX).

3. "Provide evidence that the drug product is a solution."

The applicant makes reference to the *USP* definitions for "Solutions" and "Topical Solutions" which serve to describe the dosage form of adapalene covered in this NDA. It was out of consideration of the *USP* pharmaceutical dosage form definitions that the solution designation was found applicable in lieu of using the European "Lotion" terminology. This, of course, was explained in our March 19, 1993 cover letter to the application.

Adapalene Solution, 0.1% is a dosage form where the drug substance, adapalene, is dissolved in a mixture of two mutually miscible solvents, Polyethylene Glycol 400 (a polyol) and Alcohol. The solubility of adapalene in Polyethylene Glycol 400 is mg/g and in Alcohol is mg/g, which provides a solubility in the vehicle of mg/g. Since the concentration of the finished dosage form is 1 mg/g, the adapalene is completely dissolved in the vehicle. The data provided for seventeen stability lots show that the product is a clear, homogeneous liquid with no evidence of precipitation. The first two stability lots did exhibit suspended particles but these were no longer observed after a .μ filter was employed in the final filtration step. Although the particles were not identified it was evident they were not particles of drug substance since filtration did not alter the concentration of active ingredient. It is thus the applicant's conclusion that the drug product is a solution by *USP* definition.

4. "Provide a statement that all Pharmacology/Toxicology studies have been performed using acceptable/state-of-the-art protocols which also address agency animal welfare concerns."

Please find, enclosed, a signed statement which addresses GLP compliance and animal welfare concerns. ATTACHMENT C
This matter was discussed between Dr. Browder, FDA, and Dr. Hensby, Galderma.

5. "Provide SAS Data Tapes."

   The applicant encloses two 3.5" diskettes with Ms. Rosemary Cook's "Desk Copy" for submission to the statistical reviewer.

   One diskette contains the "Merged Data Sets" and the other contains the "Raw Data Listings" for the six pivotal clinical studies. Please refer to ATTACHMENT D.

6. "Submit an integrated table which lists all the investigational formulations, reference products and the proposed commercial formulation with corresponding clinical and biopharmaceutic studies which employed the formulations."

   Please find with ATTACHMENT E four tables which summarize the product formulations both qualitatively and quantitatively. Please note it is the applicant's scientific and technical opinion that there are no significant or practical differences in the solution vehicle (base) formulations and that only the active ingredient strengths vary for dose assessment.

7. Ms. Cook also made some observations regarding expressions of human dose multiples in the labeling which will be taken up for discussion at a later date.

We would also like to draw your attention to the company name and logo change. While we have implemented use of the revised letterhead, I am awaiting official certification documents from our legal department before submitting a formal announcement amendment. I expect to provide this change notification information within the next thirty days.

I would like to express my appreciation for Ms. Cook's help with this filing review and to all other reviewers who have assisted us with clarification of specific requests.

Sincerely,

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs

DESK COPY: Ms. Rosemary Cook

GALDERMA

DUPLICATE

May 21, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
DIFFERIN Solution, 0.1%
(Adapalene Topical Solution)
Response to Special Request - Statistical and Microbiology

Dear Sir or Madam:

Reference is made to two telephone calls from Ms. Rosemary Cook, FDA Project Coordinator, on May 11 and 12, 1993. This amendment responds to the requests as follows:

Statistical Reviewer Request

1) Please find enclosed a location index and listings of important variables to assist in the use and review of the SAS datasets previously submitted.

2) We are in the process of obtaining the SAS programs and original SAS datasets from the three different organizations Galderma, Alcon Laboratories and involved in generating the datasets. These files will be sent as soon as possible.

Microbiology Reviewer Request-Microbial Limit Test

Please find enclosed a technical report (No. 064:33410:0688) which describes the Microbiological preparatory testing conducted with samples of Adapalene Topical Solution, 0.1%. The testing demonstrates that the drug product will not inhibit the multiplication, under Microbial Limit Test conditions, of microorganisms that may be present. Test results for the pilot production batches (FBGF,FBGG and FBGH) were previously provided in the April 29, 1993 amendment.

GALDERMA LABORATORIES, INC.
SUITE 200 3000 ALTA MESA BLVD P.O. BOX 901003 FORT WORTH TX 76160 817 560 2000

If either reviewer has any questions about the information provided, please give me a call.

Sincerely

Christine Shank
Manager, Regulatory Affairs
Telephone (817)551-8516

CES/sam
Enclosure

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

GALDERMA

DUPLICATE

NEW CORRESP

June 9, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
DIFFERIN Solution, 0.1%
(Adapalene Topical Solution)
Response to Special Request - Statistical and Chemistry

Dear Sir or Madam:

Reference is made to two requests received via telephone calls from Ms. Rosemary Cook, FDA Project Coordinator.

- May 11, 1993 - Request for SAS programs used in the clinical safety and efficacy analyses.

- June 7, 1993 - Request to provide a copy of the Chemistry, Manufacturing and Controls Section of the NDA to the San Antonio Resident Inspection Post with regard to inspection of the DPT Laboratories, Inc. manufacturing and control facilities.

Please find enclosed the following information in response to the two requests.

- Statistical Request - The applicant submits herewith a listing of the SAS programs that were used to generate the safety and efficacy data and a diskette of the programs. The diskette has been provided to Ms. Rosemary Cook for transmittal to the statistical reviewer. This submission fulfills the second part of the request made on May 11, 1993. Our submission of May 21, 1993 responded to the reviewer's request for a location index and listing of key variables.

- Chemistry Request - The applicant has sent to Mr. Joel Martinez, FDA San Antonio Resident Inspection Post, a complete copy of Volumes 1.1, 1.2 and 1.3 and all related Amendments on Chemistry, Manufacturing and Controls. Please find enclosed for reference a copy of our letter of transmittal.

GALDERMA LABORATORIES, INC.

SUITE 300, 3000 ALTA MESA BLVD P.O. BOX 331323, FORT WORTH, TX 76163 (817) 263-2600

We hope you find the information satisfactory and complete. Please contact me if there are any questions.

Sincerely,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone : (817) 551-8516
FAX: (817) 763-5863

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

GALDERMA

NEW CORRESP.

June 22, 1993

DUPLICATE

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUGS
REC'D
JUN 24 1993
HFD-520
EVALUATION AND RESEARCH

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Response to Special Request - Clinical

Dear Sir or Madam:

Please find enclosed a copy of our correspondence to Dr. Antoine El Hage, Clinical Investigations Branch (HFD-344), which responds to his request of June 11, 1993.

The enclosed documents are submitted to update the file. While the information is not new, it has been formatted to respond to Dr. El Hage's special request.

Sincerely

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

CES/sam
Enclosures

GALDERMA LABORATORIES, INC.
SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 337329 FORT WORTH, TX 76162 (817) 263-2500

GALDERMA

NDA ORIG AMENDMENT

DUPLICATE

July 1, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 0 2 1993
HFD-520

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Response to Chemistry Review Comments

Dear Sir or Madam:

Reference is made to a FAX from Ms. Rosemary Cook, Project Manager, dated June 14, 1993. The message consisted of two elements:

1) Transmittal of three Chemistry Review comments; and,

2) Notification that the Center for Drug Evaluation and Research Labeling and Nomenclature Committee has judged the proposed tradename "DIFFERIN" to be unacceptable.

Please find as follows our responses to all items and issues relative to the faxed message.

As regards the tradename issue, we acknowledge the agency's objections and will take the matter under further consideration. Our determination in this regard will be communicated at a later date. In the meantime, all communications will simply refer to the product as Adapalene Topical Solution, 0.1%.

Subsequent to receipt of the three Chemistry Review items, I spoke with Mr. Jim Timper, FDA Review Chemist, about the labeling issues raised in the third comment of the FAX. While it remains unclear exactly what Mr. Timper would prefer, we offer our best interpretation of the requirements and regulations. It is also our position that if the agency wants to specify the exact wording for these two labeling issues we would be happy to comply.

GALDERMA LABORATORIES, INC.

SUITE 300 3000 ALTA MESA BLVD P.O. BOX 331229 FORT WORTH, TX 76163 817 263-2600

Please find attached our response to the three Chemistry Review items.

Please contact me if there are any questions about these responses.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone (817) 551-8516
FAX (817) 763-5863

Desk Copy: Ms. Rosemary Cook
HFD-520, Room 12B-05

CES\tb

GALDERMA

DUPLICATE

April 1, 1994

Jonathan Wilkin, M.D.
Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%

CMC Review - Re-inspection of Drug Product Manufacturer

NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%

CMC Review - Pre-approval Inspection of Drug Product Manufacturer

Dear Dr. Wilkin:

Reference is made to the pending Adapalene Topical Solution and Gel New Drug Applications 20-338 and 20-380 respectively.

With specific regard to the Chemistry, Manufacturing and Controls Review of the applications, this amendment advises the reviewer that an inspection of DPT Laboratories, Inc., the manufacturer of the drug products, was conducted February 22 - March 11, 1994 and concluded on March 16 in a wrap-up meeting between the FDA inspectors and DPT, Inc. management. At the March 16 meeting a Form FDA 483 summary of inspectional observations was issued to the firm.

During the inspection we, Galderma Laboratories, Inc., were notified by DPT, Inc. that the FDA had been given instructions to cover a variety of agency interests:

- re-inspection for NDA 20-338, adapalene solution
- pre-approval inspection for NDA 20-380, adapalene gel
- comprehensive cGMP inspection
- other applications not sponsored by Galderma

APR 5 1994

As a result, the Form FDA 483 covered all aspects of the inspection. Only those observations related specifically to the adapalene applications were provided to Galderma. On March 29, 1994, DPT, Inc. formally submitted a response to all of the Form FDA 483 observations. Thus you will find enclosed for reference:

- a copy of the 483 observations on adapalene only; and,
- DPT Laboratories, Inc. March 29, 1994 response submission. (Please note that DPT, Inc. provided us a "purged" copy to protect proprietary information.)

It is our understanding that the inspection report and recommendations will be made available to the chemistry reviewer. If we can, however, be of any assistance with questions or concerns please contact us.

Field Copy Certification: "A Field Copy of this amendment, in its entirety, is provided to the FDA Dallas District Office which is the home office for the applicant and the drug product manufacturer, DPT Laboratories, Inc., San Antonio, Texas."

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817)263-2676
FAX: (817)263-2667

FIELD COPY: Dallas District Office
3032 Bryan Street
Dallas, Texas 75204

DESK COPY: Ms. Rosemary Cook
HFD-540, Room 12B-05

GALDERMA

ORIGINAL

BL

April 4, 1994

Ms. Rosemary Cook
FDA/CDER
Division of Topical Drug Products (HFD-540)
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

APR 5 1994

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
DRAFT LABELING

NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%
DRAFT LABELING

Dear Rosemary:

Reference is made to our meeting on March 23, 1994. As you requested, please find inclosed current DRAFT LABELING for the subject drug products. A 3.5 diskette with text in WORDPERFECT 5.1 is also provided for your use. The diskette contains text identical to the "hard copy" which consists of the following:

NDA 20-338 Adapalene Topical Solution, 0.1%
Primary and secondary package labeling
Physician Package Insert

NDA 20-380 Adapalene Topical Gel, 0.1%
Primary and secondary package labeling
Physician Package Insert

An archival copy of this submission has been sent to each of the pending application files. The archival copies contain three extra sets of labeling for reference and review.

Please contact me if you have any questions.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817)263-2676
FAX: (817)263-2667

Archival Copy with three (3) extra sets of labeling
DESK COPY: Ms. Rosemary Cook (HFD-540)

GALDERMA LABORATORIES, INC.
SUITE 300 2000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

GALDERMA

ORIG AMENDMENT

BC

April 26, 1994

ORIGINAL

Jonathan Wilkin, M.D.
Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

APR 2 3 1994
EVALUATION AND RESE

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
CMC Review - Drug Substance Manufacturer Inspection

NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%
CMC Review - Drug Substance Manufacturer Inspectio

Dear Dr. Wilkin:

Reference is made to the pre-approval inspection of the bulk drug substance manufacturer for adapalene in relation to the Chemistry, Manufacturing and Controls Review of NDA 20-338 for Adapalene Topical Solution, 0.1% and NDA 20-380 for Adapalene Topical Gel, 0.1%.

The inspection was conducted by Mr. Eric Thostesen, FDA International and Technical Operations Branch, on January 24 - 25, 1994 at the facilities At the conclusion of the inspection, the firm was issued a Form FDA-483.

This amendment to the pending applications serves as notification to the chemistry reviewer that has submitted a comprehensive response to each of the inspectional observations. The response and corrective action plan was forwarded to the FDA International and Technical Operations Branch on April 11, 1994. Enclosed for reference is a complete copy of the submission.

With this amendment the applicant, Galderma Laboratories, Inc., has provided all data and information currently requested or required for completing the chemistry, manufacturing and controls review of these pending applications. If however there are any additional questions or concerns, we would appreciate the opportunity to speak directly with the reviewer in order to effect resolutions as quickly as possible.

Sincere regards,

Christine Shank

Christine Shank
Manager Regulatory Affairs
Telephone (817) 263-2676

DESK COPY: Ms. Rosemary Cook
HFD-540, Room 12B-05
(Correspondence Only)

GALDERMA

DUPLICATE

BZ

June 15, 1994

Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
Adapalene Topical Solution, 0.1%
CMC Amendment

Dear Sir or Madam:

Reference is made to our pending New Drug Application for Adapalene Topical Solution, 0.1%. As the "User Fee" anniversary date, June 24, 1994, is rapidly approaching, we are making every effort to ensure that complete responses are provided to all issues and requests. With this amendment we are responding to the remaining two requests relating to the Chemistry, Manufacturing and Controls review of the application.

- A copy of the May 30, 1994 response made by Finorga SA, the drug substance manufacturer, to the FDA International and Technical Operations Branch letter dated May 9, 1994 is provided. The Finorga SA response should effectively clarify the issues and confirm compliance of the manufacturer.

- A complete response is provided to the FDA Testing Laboratory comments and requests received by FAX on May 24, 1994. The sponsor acknowledges the agency comment that while the methods will not be revalidated for NDA 20-338, a resubmission of the methods validation package for NDA 20-380 is necessary. A separate submission will of course be sent to NDA 20-380.

We believe the information provided herein is complete and that it satisfactorily addresses all issues and comments. If, however, the reviewer has any questions please contact us as we would like to resolve matters as efficiently as possible.

GALDERMA LABORATORIES, INC.

SUITE 300 3000 ALTA MESA BLVD. P.O. BOX 331229, FORT WORTH, TX 76163 (817) 293-2600

LDERMA

Field Copy Certification: "A Field copy of this amendment, in its entirety, is provided to the FDA Dallas District Office which is the home office for the applicant and the drug product manufacturer, DPT Laboratories, Inc., San Antonio, Texas."

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs

Telephone: (817)263-2676

DESK COPY: Ms. Rosemary Cook,
HFD-540

NDA 20-338

GALDERMA

November 10, 1994

Mr. Jim Timper
FDA/CDER
Division of Topical Drug Products (HFD-540)
ATTENTION: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338 / Amendment
Adapalene Topical Solution, 0.1%

NDA 20-380 / Amendment
Adapalene Topical Gel, 0.1%

Dear Mr. Timper:

This amendment to our two pending New Drug Applications for Adapalene Topical Solution and Gel provides additional information on Adapalene drug substance.

Identification of a Synthetic Impurity of Adapalene

The sponsor submits herein a technical report [No. 3203] which summarizes the laboratory evaluations relative to identification of Impurity This previously unidentified impurity was observed in four of the batches of Adapalene which were used in preclinical, clinical and drug product stability studies. The report provides a proposed chemical structure for and concludes that it is a hydroxylated derivative of Adapalene (CD271).

The **Purity by HPLC** specification for Adapalene drug substance remains:

%
No single identified impurity %
No single unidentified impurity %
Total impurities %

Response to September 29-30, 1994 FDA Form 483 Inspection Observations

Please find enclosed a copy of the response to the Form 483 inspection observations submitted by the drug substance manufacturer, to the FDA International and Technical Operations Branch (HFC-134) on October 27, 1994. This document is complete for all observations made on the Form 483 as a result of the agency's follow-up inspection of operations on September 29-30, 1994.

We, the sponsor and , believe that the responses to both the January 24-25, 1994 inspection and this follow-up inspection satisfactorily resolve the GMP compliance concerns for manufacture and control of the drug substance.

GALDERMA LABORATORIES, INC.
SUITE 300 3200 ALTA MESA BLVD P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

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Field Copy Certification: A field copy of this amendment, in its entirety, is provided to the FDA Dallas District Office which is the home office for the applicant. This certification is made pursuant to 21 CFR 314.60 (c) of the regulations.

Thank you for your time and consideration of this additional information.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone (817)263-2676
Fax (817)263-2667

DESK COPY: Mr. Jim Timper
HFD-520, Room 12B-30
(complete copy)

FAX COPY: Ms. Rosemary Cook
HFD-540
(letter only)

GALDERMA

ORIGINAL

January 11, 1995

Ms. Rosemary Cook
FDA/CDER
Division of Topical Drug Products (HFD-540)
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

RE: NDA 20-338 and NDA 20-380
Status update

Dear Rosemary:

Thank you for calling yesterday. I have assembled copies of the cover letters dating from the first of June 1994 to present for the amendments to each of the adapalene applications. Also find as follows a brief description of each amendment.

Adapalene Topical Solution, 0.1% NDA 20-338

June 3, 1994 - Revised draft labeling amendment
This was a redraft in response to FDA review comments dated 5/20/94.

June 15, 1994 - CMC amendment
- response to the FDA International and Technical Operations Branch letter dated 5/9/94.
- Response to FDA Testing Laboratory comments dated 5/24/94 regarding test procedures and methods validation.

September 2, 1994 - Methods Validation Package
At the request of the a current methods validation package was assembled and sent to the laboratory.

November 10, 1994 - CMC amendment
- Technical report provided on identification of previously unknown impurity in the drug substance.
- Copy of responses to Form 483 items from September 29-30 reinspection.

GALDERMA LABORATORIES, INC.
SUITE 200 2000 MESA RD P.O. BOX 221329 FORT WORTH TX 76163 (817) 263-2600

GALDERMA

Adapalene Topical Gel, 0.1% NDA 20-380

June 3, 1994 - Revised draft labeling amendment
This was a redraft in response to FDA review comments dated 5/20/94.

June 16, 1994 - CMC amendment

- response to the FDA International and Technical Operations Branch letter dated 5/9/94.
- Response to FDA Testing Laboratory comments dated 5/24/94 regarding test procedures and methods validation.

November 10, 1994 - CMC amendment

- Technical report provided on identification of previously unknown impurity in the drug substance.
- Copy of responses to Form 483 items from September 29-30 reinspection.

As we also discussed, I have been working with Jim Timper to resolve the CMC concerns relating to these two applications. I believe our most significant and frustrating problem is ascertaining what the International and Technical Operations Branch is doing with the information they have on the drug substance manufacturer. There have already been two inspections (the latest reinspection was done on September 29-30, 1994) and neither Jim Timper nor I have been able to find out what action will be taken next. has submitted responses to all Form 483 items and have made all requested commitments.

I hope you find this information helpful. I look forward to hearing from you soon on the status/progress of these applications.

Thank you again for checking into this matter.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone (817) 263-2676

DUPLICATE

GALDERMA

February 21, 1995

NDA ORIG AMEND

Ms. Rosemary Cook
Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
Adapalene Topical Solution, 0.1%

NDA 20-380
Adapalene Topical Gel, 0.1%

Information Amendment

FEB 22 1995
RECEIVED
EVALUATION AND RESEARCH

Dear Rosemary,

As a follow-up to the information I sent you on January 12, 1995, I thought you might also be interested in the worldwide approvals and marketing initiatives for Adapalene Topical Gel and Solution. We are very pleased to have approvals in several key European countries that are strategic to the company's marketing initiatives for the finished dosage forms of this new chemical entity. Our most recent approvals were received from the Canadian Health Protection Branch on January 24, 1995 after 19 months and 14 months review for the solution and gel applications respectively. A listing of the approvals by country is provided as follows:

Adapalene Topical Solution, 0.1%

Country	Trade Name	Application/ Authorization No.	Approval Date
Canada	DIFFERIN	9427-G0588-25	January 24, 1995
France	DIFFERIN	NL 18 083 335 238-9 (30 ml) 335 239-5 (60 ml)	July 3, 1992
Germany	DIFFERIN	Zul.Nr. 27599.00.00	July 29, 1993
Ireland	DIFFERIN	PA 590/6/1	October 19, 1993
United Kingdom	DIFFERIN	PL 10590/0014	December 5, 1994

GALDERMA LABORATORIES, INC.
SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2800

GALDERMA

Adapalene Topical Gel, 0.1%

Country	Trade Name	Application/ Authorization No.	Approval Date
Canada	DIFFERIN	9427-G0558-26	January 24, 1995
France	DIFFERIN	NL 19 410 337 887-4 (30g)	September 26, 1994
Ireland	DIFFERIN	PA 590/6/2	November 14, 1994

You may recall that the French and Irish labeling for DIFFERIN (adapalene) Topical Solution, 0.1% was submitted to NDA 20-338 in an amendment dated January 17, 1994. I am enclosing with this amendment the recently approved Canadian Product Monograph which covers both the solution and gel dosage forms of adapalene for your review and reference.

To date, neither finished dosage form has been introduced commercially in any country. As a tribute to the research and development of the drug substance by our R&D facility in France, the initial commercial launch of DIFFERIN (adapalene) Topical Gel, 0.1% will begin in France in early fall of this year.

We hope you will find this information useful in your continued efforts to evaluate our pending drug product applications We are of course most anxious to hear from you on the progress of these reviews. Please be advised that archival copies of this amendment have been submitted to each application file along with four extra review copies.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817) 263-2676

GALDERMA

ORIGINAL NC

March 21, 1995

Ms. Rosemary Cook
Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
Adapalene Topical Solution, 0.1%

NDA 20-380
Adapalene Topical Gel, 0.1%

CMC Review - Inspection Status

MAR 23 1995

Dear Rosemary:

Pursuant to our telephone conversation last Friday, March 17, I have confirmed that Finorga S.A. was contacted by the FDA International and Technical Operations Branch (ITOB) in early February requesting dates for a "general" inspection of the facility in mid-March. responded via FAX confirming March 13, 14 and 15 as possible dates. The firm also inquired if the request for reinspection was related to adapalene drug substance. A second call from FDA/ITOB confirmed that the reinspection request was related to adapalene. then advised that the process validation for adapalene would not be complete in time for the planned mid-March inspection. In a third call to . from FDA/ITOB, it was communicated that the reinspection would be planned after validation was completed.

I would like to comment that while we understand that full validation of the production process is not required for approval, it appears from the previous two inspections (January 24 - 25, 1994 and September 29 - 30, 1994) that the inspectors expect validation to be complete and have on each occasion cited the lack of process validation for commercial batches as Form 483 observations. It is this concern that dictates postponement of yet again another reinspection until the firm believes the validation to be complete and satisfactory.

Please also be advised that Mr. Jim Timper telephoned me several times yesterday in an attempt to help sort out the reinspection issues and concerns. He confirmed that FDA/ITOB does indeed intend to reinspect the operations relative to adapalene

GALDERMA LABORATORIES, INC.
SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

GALDERMA

raw material production. He spoke with personnel in ITOB, Ms. Nancy Haggard and Mr. Gary Seaborn, and has requested to meet with the inspector prior to this reinspection. As the inspector assigned this time is again different from the two previous inspectors, we feel it is essential that Mr. Timper's meeting request be honored.

On the last call, Mr. Timper had me speak with Mr. Seaborn regarding scheduling for the reinspection. It was suggested that the week of May 22 would be a good time for the inspector. I advised that based on my knowledge of validation plans that that time might be acceptable but that Mr. Seaborn should contact to make appropriate arrangements.

I would like to hear from you how this timing and reinspection fits in with the overall agency activities regarding these NDAs. Do you have a new "user fee" date or some such target date for completing your activities? Please give me a call.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817) 263-2676
Facsimile: (817) 263-2667

Copies: Archival NDA 20-338 and NDA 20-380
Ms. Rosemary Cook (HFD-540) Fax
Mr. Jim Timper (HFD-520) Fax

GALDERMA

Orig
BC

May 1, 1995

Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
Adapalene Topical Solution, 0.1%
Chemistry, Manufacturing and Controls Amendment

Dear Sir or Madame:

Reference is made to a telephone conference call with Ms. Rosemary Cook and Mr. Jim Timper, FDA representatives, and Mr. Raymon McElhaney and Ms. Christine Shank, sponsor representatives, on April 21, 1995.

Based on our understanding of the issues discussed, the following items are provided to correct all outstanding deficiencies regarding chemistry, manufacturing and controls for the drug substance, adapalene, and the drug product, DIFFERIN (adapalene) Topical Solution, 0.1%.

- Withdrawal of reprocessing provisions for the bulk drug product. Batch adjustment provisions proposed for minor adjustments only in the concentrations of the two miscible solvents.

- Adapalene drug substance process validation report from

- Additional minor proposal to omit external frosting of the glass bottles in the drug product to permit application of adhesive labels.

Please note that the sponsor is able to provide a copy of the process validation report for Adapalene drug substance. In a letter to the FDA Drug Master File Staff dated April 24, 1995, advised that a revised DMF for adapalene has been submitted in addition to the process validation report. As the sponsor was not given a copy of the revised DMF, we can only request incorporation of this information in support of the NDA as previously authorized by To the best of our knowledge (per contacts with by Galderma the revised DMF incorporates all the relevant changes that resulted from responses to the FDA Form 483 inspection observations (NDA Amendments dated April 26, 1994; June 15, 1994 and November 10, 1994).

GALDERMA LABORATORIES, INC.
SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

We sincerely appreciate Mr. Timper's advice, supportive concern and assistance towards a satisfactory resolution of the CMC issues. Please contact me if there are any questions.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817) 263-2676
Facsimile: (817) 263-2667

Field Copy Certification: A field copy of this amendment, in its entirety, is provided to the FDA Dallas District Office which is the home office for the applicant and the drug product manufacturer, DPT Laboratories, Inc., San Antonio, Texas. This certification is made pursuant to 21 CFR 314.60(c) of the regulations.

Christine Shank

Christine Shank, Manager Regulatory Affairs

cc: Archival
Review
Ms. Rosemary Cook (faxed copy of cover letter only)

GALDERMA

HC
3/25 94

ORIGINAL

March 2, 1994

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
Adapalene Topical Solution, 0.1%
Authorization Letter

Dear Sir or Madam:

Reference is made to a request by Dr. Karl Lin (HFD-715) for submission of electronic data from the carcinogenicity studies provided in NDA 20-338.

Due to the urgency of the request and the overseas location, England, of the Laboratory responsible for the original data, we believe that submission of the electronic data can be expedited if sent directly to Dr. Lin's attention. The sponsor, Galderma Laboratories, Inc., of NDA 20-338 therefore confers authorization to to communicate directly with Dr. Karl Lin and submit the requested electronic data on behalf of the sponsor. In turn will provide to the sponsor a complete copy of all correspondence with Dr. Lin for formal submission to the NDA file.

We appreciate the agency's cooperation in regards to this matter.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817)263-2676

cc: Mr. Frank W. Ross
Head, Toxicology Operations
Pharmaco::LSR
Eye
Suffolk IP23 7PX
ENGLAND

FAX Copy: Ms. Rosemary Cook
HFD-520, Room 12B-05

ORIGINAL

GALDERMA

BP

NDA ORIG AMENDMENT

March 18, 1994

Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
PRE-Clinical/Statistical Review

Dear Sir or Madam:

Reference is made to a request via telephone call from Ms. Rosemary Cook, FDA Project Manager, in late February 1994, for submission of the pathology (tumor) data, in electronic format, from the two rodent carcinogenicity studies submitted in NDA 20-338.

Pursuant to the request, the contract laboratory that conducted the studies, , prepared the electronic data files and submitted the diskettes and supporting documentation directly to Dr. Karl Lin (HFD-715) on March 10, 1994. Thus, this submission to the file is formal notification of the transfer of the electronic data to the statistical reviewer and submission of the supporting documentation.

Since we have been unable to determine any specifics with regard to the pre-clinical review and since there is some question on our part about requirements for additional data, we can only assume that this submission fulfills the current request as we understand it.

We sincerely hope the data and documentation provided will prove useful and satisfactory.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs

Enclosures: Archival Copy
Pharm/Tox Review Copy
Extra Copy

DESK COPY: Ms. Rosemary Cook
HFD-540
(cover letter only)

GALDERMA

NDA ORIG AMENDMENT

DUPLICATE

August 12, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Chemistry, Manufacturing and Controls - Response to Form FDA 483 Inspectional Observations

Dear Sir or Madam:

Reference is made to the FDA inspection, conducted June 28 through July 2, 1993, of the DPT Laboratories, Inc., San Antonio, Texas manufacturing and quality control facilities and operations. The inspection was specifically related to production and control of the drug product, Adapalene Topical Solution, 0.1%, covered under pending NDA 20-338. At the conclusion of the inspection, a notice of inspectional observations (Form FDA 483) was issued to DPT Laboratories, Inc. This amendment thus provides a copy of the official response prepared by DPT Laboratories, Inc. to each of the Form FDA 483 observations. Please be advised that Galderma Laboratories, Inc. provided assistance to DPT. Inc. in assessment of the procedural and technical issues.

GALDERMA LABORATORIES, INC.
[illegible]

Based on our understanding of the inspection observations and the DPT, Inc. responses, it is our conclusion that DPT Laboratories, Inc. has provided sufficient documentation and evidence of their ability to manufacture and control the finished drug product in accordance with the methods and procedures described in the pending NDA and in compliance with all applicable good manufacturing practices regulations. In the event the chemistry reviewer has any questions regarding the technical aspects of the methods and procedures proposed in the NDA, the sponsor will be happy to assist.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone 817/263-2676

DESK COPY (correspondence only):
Ms. Rosemary Cook
HFD-520, Room 12B-05

Wilson H. DeCamp, Ph.D
HFD-520, Room 12B-10

GALDERMA

DUPLICATE

NDA ORIG AMENDMENT

September 17, 1993

David Bostwick
Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG
REC'D
SEP 20 1993
HFD-520
EVALUATION & RESEARCH

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%

Dear Mr. Bostwick:

Reference is made to our telephone conversations on September 14 and 16. Please find enclosed our responses to each of the questions as discussed. I think you will find everything in order, but please give me a call if you have any further questions or comments.

Also, I am in receipt of your FAX today with the statistical format from Dr. Harkins. We will contact Ralph directly if we have any questions in this regard.

Sincerely

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs
Telephone (817)263-2676
FAX (817)263-2667

DESK COPIES: Mr. David Bostwick
HFD-520, Room 12B-45

Ms. Rosemary Cook
HFD-520, Room 12B-05

GALDERMA

ORIGINAL

B2

CERTIFIED MAIL P 378 566 801
Return Receipt Requested

September 24, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Clinical and Statistics

Dear Sir or Madam:

Please find enclosed, data tables for clinical study 9104-CD271-EV, formatted according to a request received from Mr. David Bostwick and Dr. Ralph Harkins via FAX of September 17, 1993. Please note Clinical Review and Statistical Review copies are provided.

Please contact me if there are any questions regarding this submission.

Sincere regards,

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs
Telephone (817)263-2676

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

ES/sm
Enclosure

GALDERMA

NEW CORRESP

ORIGINAL

CERTIFIED MAIL # P 378 566 857
Return Receipt Requested

September 24, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
Adapalene Topical Solution, 0.1%

NDA 20-380
Adapalene Topical Gel, 0.1%

Dear Sir or Madam:

We acknowledge receipt on September 20, 1993, of a FAX from Ms. Rosemary Cook, FDA Project Manager, containing Chemistry Review comments relative to NDA 20-338. We further acknowledge that, in principle, some of the comments can also be considered relevant to NDA 20-380.

The applicant has reviewed these comments with management and personnel at DPT Laboratories, Inc., and agree that a full response can be submitted by October 29, 1993. We appreciate the opportunity to contact the reviewer, Mr. Timper, for clarification and/or assistance in understanding the comments as necessary.

Sincere regards,

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

GALDERMA LABORATORIES, INC.
SUITE 300. 3000 ALTA MESA BLVD., P.O. BOX 331329. FORT WORTH, TX 76163 (817) 263-2600

GALDERMA

NDA CHANGE MENT
AC

October 29, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Chemistry, Manufacturing and Controls Data

Dear Sir:

Reference is made to a FAX dated September 20, 1993, from Ms. Rosemary Cook, FDA Project Manager, which itemized ten (10) review comments regarding the chemistry, manufacturing and controls for Adapalene Topical Solution, 0.1% and the drug substance, Adapalene.

Please find enclosed a complete response to each of the review comments with the exception of Comment 1. As I discussed with Ms. Rosemary Cook on October 22, we were unexpectedly delayed in our efforts to complete methods validation for the Chromatographic Purity and THF assay procedures by the October 29 commitment date. Thus, the laboratory reports for Adapalene drug substance lots being analyzed by DPT Laboratories are incomplete for theses two tests at this time. I have advised Ms. Cook in a FAX dated October 27, that we anticipate a submission of these missing elements on or before November 24, 1993.

Please also note that when we make the November submission, we will resubmit a complete and comprehensive Methods Validation Package (in triplicate) for all regulatory procedures used for control of the drug substance and drug product. In this submission you will find in Volume 2 of 2, copies of the new and revised/corrected procedures from the responses. Two extra copies of Volume 2 of 2 are provided for your use as needed.

I hope you will find the information and data provided herein complete and satisfactory. We are, of course, pursuing completion of the methods validation for the two assays for submission at the earliest opportunity. Please give me a call if you should have any questions about the information in this submission or if you need to discuss any concerns or issues.

Sincere regards,

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs
Telephone: (817)263-2676
FAX: (817)263-2667

cc: Ms. Rosemary Cook
HFD-520, Room 12B-05
(correspondence only)

Dallas District Office
3032 Bryan Street
Dallas, Texas 75204
(Volumes 1 and 2)

CES/sm

GALDERMA

DUPLICATE

NDA CR3 AMENDMENT

BC

October 29, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG
REC'D
HFD-520
EVALUATION AND RESEARCH

RE: NDA 20-338
Adapalene Topical Solution, 0.1%

Dear Sir or Madam:

Please find enclosed additional statistical information which was requested by Dr. Srinivasan earlier this week. Included with the desk copy of this submission is a diskette containing SAS code, which has been forwarded directly to Dr. Srinivasan.

Please contact me if you have any questions regarding this submission.

Sincerely,

Terry Isaacs

Terry Isaacs
Regulatory Affairs Associate
Telephone: (817) 263-2679

DESK COPY:

Dr. Srinivasan
HFD-713, room 15B45

GALDERMA

NDA CRO AMENDMENT
BC

November 24, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Chemistry, Manufacturing and Controls Data

Dear Sir:

Reference is made to a FAX dated September 20, 1993 from Ms. Rosemary Cook, FDA Project Manager, which itemized ten review comments regarding the chemistry, manufacturing and controls for Adapalene Topical Solution, 0.1% and the drug substance, Adapalene. Reference is also made to our amendment submission dated October 29, 1993 which provided complete responses to each of the review comments with the exception of Comment 1.

Pursuant to our October 29, 1993 commitment, this amendment provides the following documentation:

1. Revised analytical procedures and associated methods validation documentation for assay of residual tetrahydrofuran and chromatographic purity for adapalene drug substance.

2. Completed analytical reports for three lots of drug substance. The analyses conducted by DPT Laboratories, Inc. using the specified regulatory methods, confirm the drug substance manufacturer's certificates of analysis and demonstrate DPT's ability to perform all the regulatory tests.

3. DPT Laboratories, Inc. procedures for assay and ID of alcohol and adapalene in the finished drug product.

4. Comprehensive Methods Validation Package for all tests, specifications, analytical methods and validation reports, as required, for control of the drug substance and finished drug product.

GALDERMA LABORATORIES, INC
SUITE 300 3000 ALTA MESA BLVD P.O. BOX 331309 FORT WORTH TX 76163 817 263-2600

The applicant submits that with this amendment and the October 29, 1993 amendment, all elements of the reviewer's comments have been fully and completely addressed. We, of course, will be grateful for the opportunity to discuss any matters of concern or question.

Also pursuant to 21 CFR 314.70 (a) and 314.71 (b) as amended by Final Rule published in the Federal Register September 8, 1993, the applicant makes the following certification:

> A Field Copy of this amendment, in its entirety, is provided to the FDA Dallas District Office which is the home office for the applicant and the drug product manufacturer, DPT Laboratories, Inc., San Antonio, Texas.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone (817)263-2676
FAX (817)263-2667

cc: Ms. Rosemary Cook
HFD-520, Room 12B-05
(correspondence only)

Dallas District Office
3032 Bryan Street
Dallas, Texas 75204
(Volumes 1 and 2)

CES/sm

GALDERMA

NDA AMENDMENT

December 3, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG
REC'D
DEC 8 1993
HFD-520
EVALUATION AND RESEARCH

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Environmental Assessment

Dear Sir or Madam:

Reference is made to a telephone conversation with Dr. Su C. Tso on July 23, 1993 regarding additional information on Environmental Assessment (EA) for Adapalene drug substance and Adapalene Topical Solution, 0.1% drug product.

Please find enclosed a complete resubmission of the EA which conforms with 21 CFR 25.31a (b)(3). The applicant has limited the EA document to non-proprietary data and information which will permit public disclosure upon approval of the pending application. All proprietary and confidential information and materials specifically requested by the reviewer have been placed in the Appendix of the EA.

Please advise if we can be of further assistance in this regard.

Sincerely,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone(817)263-2676
FAX (817)263-2667

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05
(correspondence only)

Su C. Tso, Ph.D.
Environmental Staff, HFD-520
Room 12B-10
(complete copy)

GALDERMA

BC

December 10, 1993

James Timper, Chemist
FDA/CDER
Division of Anti-Infective Drug Products (HFD-520)
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Chemistry, Manufacturing and Controls

Dear Mr. Timper:

Reference is made to your FAX dated December 8, 1993. Please find as follows our response to your two questions.

1. A resubmission of Environmental Assessment was provided on December 3, 1993. The EA and accompanying appendix included all information requested by Dr. Tso in her July 23, 1993 memorandum. The Document Control Room should be in receipt of the submission by this date.

2. In response to your second inquiry, arrangements have been made for DPT Laboratories, Inc. to provide to the inspectors, if requested, samples of three of the impurity compounds listed on page 3 0022, Volume 1.1 of the NDA:

   Impurity (only a few milligrams available)
   Impurity
   Impurity

   Impurity is of unknown structure and is unavailable, to our knowledge, either from or DPT Laboratories, Inc. Since refinement of the drug substance manufacturing process by Impurity is no longer a potential impurity. Impurity , which was also of unknown structure, has not been detected in any of the industrial batches and was detected only in one very early development batch manufactured by I have enclosed copies of the "Impurity Profile" and Batch Analyses" summaries from the NDA for reference.

Thank you for your Faxed inquiries. I hope you will find these responses satisfactory. If you have any further questions, please do not hesitate to contact me.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
FAX (817)263-2667
Telephone (817)263-2676

Field Copy: Dallas District Office
3032 Bryan Street
Dallas, Texas 75204

Certification: "A Field Copy of this amendment, in its entirety, is provided to the FDA Dallas District Office which is the home office of the applicant and the drug product manufacturer, DPT Laboratories, Inc., San Antonio, Texas"

FAX: Ms. Rosemary Cook
HFD-520, Room 12B-05
(correspondence only)

CES/sm

GALDERMA

NEW CORRESP

January 10, 1994

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Additional Information on Environmental Assessment

Dear Sir or Madam:

Please find enclosed for the file, additional information on Environmental Assessment for NDA 20-338 requested by Dr. Su C. Tso.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs

CES/sm

GALDERMA

January 10, 1994

VIA FAX

TO: Su C. Tso, Ph.D.
Division of Anti-Infective Drug Products (HFD-520)
Telephone (301)443-4300
FAX (301)443-5803

FROM: Ms. Christine Shank
Regulatory Affairs
Galderma Laboratories, Inc.
Telephone (817)263-2676
FAX (817)263-2667

RE: NDA 20-338
Adapalene Topical Solution, 0.1%
Additional Information on Environmental Assessment

Dear Dr. Tso:

Reference is made to our telephone conversation just prior to the Christmas holidays regarding permits cited for DPT Laboratories, Inc. in the December 3, 1993 Environmental Assessment for NDA 20-338.

I contacted the DPT Laboratories, Inc. person responsible for permits and licenses and have received a more comprehensive description of each permit with expiration dates indicated as applicable. Please find with this transmission a copy of the information I received. I hope you will find this additional information satisfactory.

A formal submission is being sent to the NDA file.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs

CES/sm

GALDERMA

January 17, 1994

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Foreign Labeling and Facilities Inspection

Dear Sir or Madam:

As requested by Ms. Rosemary Cook, FDA Project Manager, please find enclosed an Archival Copy and three extra review copies (unbound) of the approved foreign labeling for Differin (Adapalene) Topical Solution, 0.1%. The two countries in which the drug product has received final approval are:

FRANCE

Application Number:	NL 18 083
Marketing Authorization No.:	335 238-9 (30mL)
	335 239-5 (60mL)
Date of Approval:	July 3, 1992

IRELAND

Product Authorization No.:	PA 590/6/1
Date of Approval:	October 19, 1993

To date, the drug product has not been introduced commercially in any foreign country.

The applicant has also received information with regard to FDA inspections of the manufacturing facilities. It is our understanding that the Field Investigations Branch has made arrangements with the drug substance manufacturer, , for inspection on January 24-25, 1994. Additionally, re-inspection of the drug product manufacturer, DPT Laboratories, Inc., San Antonio, Texas, was scheduled for the week of January 10. We can only assume there was an unavoidable delay for the inspector and that the inspection will be rescheduled at the earliest opportunity.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone (817)263-2676

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

VOLUME 1.2 - Drug Product Description
Environmental Assessment

VOLUME 1.3 - Samples and Methods Validation

Proposed labeling for the drug product (ITEM 4.c.) will be submitted with the remaining sections of the application. In addition to complete Archival and Review copies, the applicant has provided two duplicate sets of the SAMPLES and METHODS VALIDATION Sections. (ITEMS 4.a. and 4.b.) for the FDA analytical laboratories. The samples identified in this section will be made available upon request.

We appreciate the opportunity to initiate the review process for this application. It is requested that any questions or comments regarding this submission should initially be directed to my attention. I will then be able to place the reviewer in contact with the appropriate technical personnel for further discussion.

Sincerely yours,

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs
Telephone: (817)551-8516
FAX: (817)763-5863

cc: Desk Copy (Cover Letter)
Ms. Maureen Dillon-Parker
HFD-520, Room 12B-05

Mr. Stephen W. Clark
President, OWEN/GALDERMA Laboratories, Inc.

CES/sam

GALDERMA

ORIGINAL

NDA ORIG AMENDMENT

BM

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 1 1994
HFD-520

January 31, 1994

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
Clinical Data Presentation Request

Dear Sir or Madam:

Reference is made to a telephone conversation with Mr. David Bostwick on January 28, 1994. Pursuant to the discussion, please find enclosed, data tables for the U.S. Clinical studies 9104-CD271L-EV, C-88-27 and C-88-26 which present efficacy endpoint values excluding all patients taking oral antibiotics. The data tables provide, for comparison, the original report values and the adjusted values.

Reference is also made to a telephone call from Ms. Rosemary Cook on January 26, requesting a Safety Update. We are in the process of putting together a comprehensive report which I hope to submit by the end of this week

We hope you find this information satisfactory. If we can be of any further help in this regard, please contact me.

Sincerely,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817)263-2676
FAX: (817)263-2667

Desk Copy: Ms. Rosemary Cook
HFD-520, Room 12B-05

Mr. David Bostwick
HFD-520, Room 12B-45

ORIGINAL

GALDERMA

BC

July 6, 1995

NDA ORIG AMENDMENT

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12420 Parklawn Drive
Rockville, Maryland 20857

RE: NDA 20-338 / Amendment
DIFFERIN™ (adapalene) Topical Solution, 0.1%
Patent Information

NDA 20-380 / Amendment
DIFFERIN™ (adapalene) Topical Gel, 0.1%
Patent Information

JUL 11 1995

Dear Sir or Madam:

The applicant submits herewith amended information since submission of the original applications with regard to the patent which claims the drug, adapalene, and its method of use.

This submission reflects the extended patent term for U.S. Patent No. 4,717,720 under the Uruguay Round Agreements Act as well as the information required from applicants under 21 CFR 314.53 published in the Federal Register October 3, 1994.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817) 263-2676
Facsimile: (817) 253-2667

copies: Archival
CMC Review
Ms. Rosemary Cook (via FAX) HFD-540

GALDERMA

June 3, 1994

Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

DESK COPY
Rosemary Cook

RE: NDA 20-338/Amendment
Adapalene Topical Solution, 0.1%
DRAFT LABELING - Revised May 1994

NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%
DRAFT LABELING - Revised May 1994

Dear Sir or Madam:

Reference is made to the "Draft" physician insert labeling for Adapalene Topical Gel, 0.1% (NDA 20-380) provided to us via FAX on 5/20/94. As we were advised by Ms. Rosemary Cook to use this draft as a model for the solution dosage form covered under NDA 20-338, we are enclosing our re-drafts of labeling for both dosage forms with this submission. Reviewers will note that the text we propose is the same for both products except as differences in dosage form dictate in the sections for DESCRIPTION, ADVERSE REACTIONS and HOW SUPPLIED.

Since the 5/20/94 FDA draft was based only on recommendations from the medical/clinical review of NDA 20-380 and the biopharmaceutic and pharmacology reviews have not been considered, we have basically retained our original proposals for the sections relating to these other reviews. We have however adopted many of the review recommendations for the PRECAUTIONS section which suggest labeling for topical retinoids as a class. Also, where specific animal and/or human studies have demonstrated differences in the action or activity of the drug from other topical retinoids, the text has been modified to accurately reflect the differences.

Our most notable exception to the draft regards the recommendation for Pregnancy Category X. We have re-drafted this section to again propose Category C Labeling and have accurately represented the findings from the relevant animal studies. Based on the available data, we submit that our proposed labeling clearly meets the criteria for Pregnancy Category C Labeling.

GALDERMA LABORATORIES, INC.

SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

On the following pages are the applicant's comments and reasons for revisions which differ from the FDA draft recommendations. Please note that references, as applicable, are made to information in the Summary Sections of the applications in support of and documentation for the proposed revisions.

An Archival Copy is provided for each application. Review Copies are also enclosed for each review discipline.

We appreciate the agency's consideration of these amendments.

Sincere regards,

Christine Shank

Christine Shank
Manager Regulatory Affairs

Archival Copy
Review Copies (5)

DESK COPY: Ms. Rosemary Cook
(diskette included)

N 20-380

GALDERMA

July 15, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
ATTENTION: Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

RE: ADAPALENE TOPICAL GEL, 0.1%
Original New Drug Application Submission

Dear Sir or Madam:

The applicant, Galderma Laboratories, Inc., is pleased to submit herewith a New Drug Application for Adapalene Topical Gel, 0.1%. This application is submitted pursuant to Section 505 (b) of the Federal Food, Drug, and Cosmetic Act and in accordance with the procedures and requirements established in Part 314 of Title 21 of the *Code of Federal Regulations*.

The proposed new drug product is a topical gel dosage form of the new chemical entity, adapalene (*USAN*), indicated for the treatment of acne vulgaris. The drug product has been the subject of clinical investigations in the United States under IND since 1989. The approved product will be made available to patients only by prescription from a licensed physician.

Organizational Relationships and Affiliations
For clarification of the relationships of the companies involved with the development of the drug, we offer the following brief explanation. Galderma Laboratories, Inc., (formerly known as Owen/Galderma Laboratories, Inc.) Fort Worth, Texas, the sponsor of this application, and Galderma, Valbonne, France, the developer of the drug, are organizations existing under the joint ownership of Nestlé S.A. and L'Oréal. Galderma Laboratories, Inc. and Alcon Laboratories, Inc. are affiliate companies through the ownership interest of Nestlé S.A. (Alcon is a wholly owned subsidiary of Nestlé). DPT Laboratories, Inc., San Antonio, Texas (formerly known as Dermatological Products of Texas, Inc.) is independently owned and operated by Dorman-Feik Acquisitions Corp. Galderma Laboratories, Inc. contracts with DPT Laboratories, Inc. for the production, control and distribution of finished (marketed) drug products and for production and control of drug products under investigational development. The collaborative participation by these companies in the conduct of preclinical and clinical studies and in drug and formulation development is reflected in this application.

Drug Development Overview
Drug development and preclinical studies were conducted or sponsored by Galderma, Valbonne, France. Initial safety and efficacy testing (phase 1 and 2 studies) in human volunteers and acne patients was also conducted by Galderma in Europe. Subsequent phase 2 and 3 clinical investigations have been conducted in the United States under IND and in Europe. In addition to the topical gel dosage form described in this application, the drug has been investigated in solution and cream dosage forms under INDs respectively. A New Drug Application (NDA 20-338) for Adapalene Topical Solution, 0.1% was submitted on March 19, 1993 and is currently undergoing review in the Division of Anti-Infective Drug Products.

Dosage Form
The dosage form described in this application is a aqueous gel formulation containing the drug substance, adapalene, in suspension.

Special Features and Elements of the Application

- A Reviewer's Guide to the Application is provided in the introductory part of Volume 1.1 (page xvi) which describes the organizational and structural features of the document.

- Many of the administrative elements initially requested following submission of Adapalene Solution NDA 20-338, have been incorporated in this document. Reviewers will find such items as:

  a) Formulation Summary and Tabulated Summary of Formulations used in Biopharmaceutic and Clinical Studies (Volume 1.1, pages 2 0053, 2 0222 and 2 0309).
  b) List of Manufacturers and Status of Inspection Readiness (Volume 1.1, page 2 0062).
  c) Certification of Compliance with GLP Requirements and Animal Welfare Concerns (Volume 1.1, page 2 0065).
  d) Status of Clinical Studies and Compliance with Informed Consent and IRB/Ethical Committee Review Requirements (Volume 1.1, page 2 0242).

  All of these elements are listed in the Application and relevant Section Indices.

- A Certification is provided following this cover letter which establishes Galderma Laboratories, Inc. as the legal adopted name of the sponsor.

- A complete resubmission of all nonclinical pharmacology and toxicology studies provided in NDA 20-338 for Adapalene Topical Solution, 0.1%, is made since many of the studies included the topical gel dosage form. Additional studies and reports for Adapalene Topical Gel are highlighted in the Section Index in a distinctive magenta color. The introduction to the nonclinical pharmacology and toxicology section provides a concise overview of the additional studies.

FDA Meetings and Correspondence

The meetings and correspondence with the Food and Drug Administration which significantly influenced the development of this application are briefly described as follows:

- On September 19, 1989, Dr. Browder, Mr. Davitt and Dr. Osterberg of FDA met with sponsor representatives to discuss the nonclinical studies planned for submission in support of an NDA. A satisfactory agreement was reached by the participants on the list of required pharmacology and toxicology studies with the exception of the conduct of a study to assess photocarcinogenicity potential. The sponsor expressed several reasons why a photocarcinogenicity study should not be a requirement for formulated adapalene (CD 271) and in follow-up correspondence of October 27, 1989 agreed to labeling precautions as a means of addressing the matter. In a letter from Dr. Murray Lumpkin dated April 27, 1990, the agency concurred that the sponsor must provide precautionary labeling clearly stating that there have been positive findings relating to photocarcinogenicity for retinoids and related compounds. If the sponsor did not, however, elect to do precautionary labeling, then studies would be required. Preparatory to the submission of the NDA for Adapalene Topical Solution, 0.1%, the sponsor, in a letter dated December 3, 1991, reaffirmed the commitment to include a statement in the labeling. The reviewer will find that the PRECAUTIONS section of the draft labeling for the gel drug product contains wording which closely follows the statement suggested in Dr. Lumpkin's April 27, 1990 letter.

- The second meeting was a Pre-NDA meeting that took place on November 7, 1990 which included Drs. Lumpkin, Burlington, Evans, Rand, Harkins and Ms. Cook of FDA and sponsor representatives. The focus of this meeting was to review the available clinical data from both U.S. and European studies and to assess the completeness of the clinical evidence of safety and efficacy towards making a determination of fileability of an NDA for the drug product. Based on several comments and concerns expressed by agency participants with regard to the one completed vehicle-controlled study, the sponsor elected to conduct an additional vehicle-controlled study which was initiated in March, 1991 and completed in August, 1991. The submission of this application is based on the November 7, 1990 meeting discussions and the completion of the subsequent clinical study.

- October 19, 1992 correspondence to IND addressed the matter of submitting "line listings" for patients enrolled in pivotal clinical studies. The format of the computer generated listings provided in this application closely follow the recommendations and suggestions made by agency personnel.

Contact Person
Due to diverse location of key scientific and technical personnel within the organizations responsible for the contents of this application, it is requested that any questions or comments regarding this submission should be directed to the person named as follows:

Ms. Christine Shank
Manager, Regulatory Affairs
Galderma Laboratories, Inc.
P.O. Box 331329
Fort Worth, Texas 76163

Telephone: (817)263-2676
Fax: (817)263-2672

Contents of the Application
The New Drug Application for Adapalene Topical Gel, 0.1% consists of the following:

VOLUME 1.1
- Cover Letter
- Form 356h
- Letters of Authorization
- Generic Drug Enforcement Act Certification
- Applicable Patents (ITEM 13)
- Reviewer's Guide to the Application
- ITEM 1. APPLICATION INDEX
- ITEM 2. SUMMARY
- DRAFT LABELING

VOLUMES 1.2 - 1.3
- ITEM 3. CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

VOLUME 1.4
- ITEM 4.a. SAMPLES
- ITEM 4.b. METHODS VALIDATION

VOLUMES 1.5 - 1.46
- ITEM 5. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SECTION

VOLUMES 1.47 - 1.48
ITEM 6. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION
VOLUMES 1.49 - 1.78
ITEM 8. CLINICAL AND STATISTICAL DATA SECTION
VOLUMES 1.79 -1.86
ITEM 11. CASE REPORT TABULATIONS

VOLUMES 1.87
ITEM 12. CASE REPORT FORMS

The applicant extends its sincere appreciation to the agency staff and reviewers for their time spent in review and consideration of this application. We will be delighted to assist with any questions or requests for additional information.

Sincere regards,

Christine E. Shank

Christine E. Shank
Manager, Regulatory Affairs

DESK COPY VOLUME 1.1: (2 copies)
Ms. Rosemary Cook
Division of Anti-Infective Drug Products
HFD-520, Room 12B-05

cc: Mr. Stephen W. Clark
President, GALDERMA Laboratories, Inc.

CES/letter
CES/sam

GALDERMA

NDA ORIG AMDT

SU

December 15, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%
4-Month Safety Update

Dear Sir or Madam:

The sponsor submits herewith the 4-Month Safety Update to NDA 20-380 pursuant to 21 CFR 314.50 (d) (5) (vi) *(b)*. The report is comprehensive for all dosage forms of adapalene and includes information from all U.S. and foreign studies.

If there are any questions, please contact me at (817)263-2676.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs

DESK COPY: Ms. Rosemary Cook
HFD-520, Room, 12B-05

CENTER FOR DRUG
REC'D
DEC 1 6 1993
HFD-520
EVALUATION AND RESEARCH

GALDERMA LABORATORIES, INC.
SUITE 200 3000 ALTA MESA BLVD P.O. BOX 331333 FORT WORTH TX 76163 (817) 263-2600

TABLE OF CONTENTS

A. INTRODUCTION

An NDA on adapalene gel was submitted to the FDA in July of 1993. Although the NDA was specific for adapalene gel, there are a total of three dosage forms of adapalene being evaluated (gel, solution and cream). Each formulation has been studied under a separate IND. This four-month safety update for NDA 20-380 includes information on the three dosage forms of adapalene. The table below outlines the status of submissions and numbers of humans exposed to each formulation.

		NUMBER EXPOSED		
Dosage Form	Status	Healthy Volunteers	Acne Patients	
Aqueous Gel, 0.1% and 0.3%	NDA submitted (20-380)	271	661	
	New Clinical Experience	105	86	
Solution, 0.1%	NDA submitted (20-338)	199	571	
	New Clinical Experience	None	None	
Cream, 0.1%	Clinical trials completed - NDA targeted for 1994.	25	175 139	(U.S.) (European)
TOTAL:		--- 600	----- 1632	= **2232**

Since the filing of NDA 20-380, 191 additional humans have been exposed to adapalene gel. Exposure to adapalene has also increased due to the studies conducted with the cream

formulation. The labeling for adapalene gel has not been altered or revised as a result of this additional human exposure. In fact, adverse events are less frequent with the aqueous gel as compared to the solution dosage form (refer to Table 1).

B. UPDATE OF PRECLINICAL INFORMATION

1. Adapalene Gel

There have been no new preclinical toxicology studies on adapalene aqueous gel since the filing of NDA 20-380.

2. Adapalene Solution

There have been no new preclinical toxicology studies performed on adapalene solution since the filing of NDA 20-338.

3. Adapalene Cream

There have been no new preclinical toxicology studies performed on adapalene cream since the filing of IND

C. UPDATE OF CLINICAL INFORMATION:

1. Adapalene Gel

Five pharmacology studies, one systemic evaluation in healthy volunteers, and one clinical trial in acne patients have been completed since the filing of NDA 20-380 for adapalene gel. The safety profile and product labeling for adapalene were not

affected by this additional exposure. Refer to Table 2 for an overview of these studies.

The pharmacology studies revealed no new information about adapalene. In three (CR92144, CR92140 and CR92143) of the five studies, there was no evidence of cumulative irritation when used in conjunction with other anti-acne products and no phototoxicity potential. The higher (0.3%) concentration of adapalene was slightly irritating in one of the cumulative irritation studies (2017). Adapalene gel did not induce or modify the skin's reaction to irradiation as shown in study CR92141. And lastly, the ongoing systemic study (2005) has proceeded with no serious treatment-related medical events being reported.

The Phase II clinical trial (CR92142) in acne patients has been completed and the data is being analyzed. There were no serious treatment related medical events reported.

2. Adapalene Solution

There have been no new clinical (Phase I or II) trials performed on adapalene solution since the filing of NDA 20-338.

3. Adapalene Cream

Two clinical trials have been completed on the adapalene cream 0.1% dosage form since the filing of NDA 20-380. Once again, the safety profile and product labeling of adapalene solution has not been affected.

A total of 175 patients were exposed to adapalene cream in the U.S. and 139 patients were exposed in Europe. Both of the clinical trials were similar in design with the exception of the concurrent control. The U.S. study incorporated a vehicle controlled design (adapalene cream 0.1% vs. vehicle) and the European study was a reference-controlled trial (adapalene cream 0.1% vs. Retin-A Cream 0.05%).

The incidence rates of medical events were less with the cream formulation than those reported with the adapalene solution and similar to those reported for adapalene gel. However, the medical events were similar in intensity and duration during both of the cream multi-clinic trials. None of the patients were discontinued due to a serious treatment-related event.

D. UPDATE OF WORLDWIDE MARKETING APPLICATIONS

Foreign marketing applications for DIFFERIN™ (Adapalene) Topical Solution, 0.1% have been approved in France and Ireland. To date the drug, in any dosage form, has not been marketed in any country outside the U.S. The sponsor will submit approved foreign labeling in an amendment to NDA 20-338 for Adapalene Topical Solution, 0.1% hopefully in January 1994 as we are awaiting certified translation of the French labeling.

E. LITERATURE UPDATE

There have been no new published reports concerning adapalene (gel, solution, or cream.)

F. CONCLUSION

A total of 2232 healthy volunteers and acne patients have been exposed to adapalene in a gel, solution or cream dosage form. There have been no serious treatment related medical events

reported in any of these studies. The medical events reported for the three dosage forms of adapalene were similar in type, intensity and duration, but slightly less in frequency for the gel and cream forms than for the solution. This may be attributed to the alcoholic content in the solution vehicle. The new information collected from this additional human exposure did not affect the safety profile or the product labeling for adapalene gel 0.1%.

G. TABLES AND ATTACHMENTS

TABLE 1 - FREQUENCY AND INCIDENCE OF MEDICAL EVENTS

Medical Events (Dermatologic)	Adapalene Solution N=571			Adapalene Gel N=661			Adapalene Cream N=314(a)		
	# of ME's	# of Patients	Incid. %	# of ME's	# of Patients	Incid. %	# of ME's	# of Patients	Incid. %
RELATED	N	N	%	N	N	%	N	N	%
Skin Discomfort	21	21	(3.7)	4	4	(0.6)	1	1	(0.3)
Skin Irritation	14	14	(2.4)	4	4	(0.6)	5	5	(1.6)
Erythema	12	12	(2.1)	6	6	(0.9)	1	1	(0.3)
Skin Dry	11	11	(1.9)	7	7	(1.1)	1	1	(0.3)
Pruritus	8	8	(1.4)	2	2	(0.3)	0	0	-
Dermatitis	3	3	(0.5)	1	1	(0.2)	0	0	-
Sunburn	2	2	(0.3)	1	1	(0.2)	0	0	-
Acne (Flare)	1	1	(0.2)	3	3	(0.5)	2	2	(0.6)
Impetigo (Flare)	1	1	(0.2)	0	0	-	0	0	-
Edema (Eyelid)	0	0	-	0	0	-	2	2	(0.6)
POSSIBLY RELATED									
Sunburn	8	7	(1.2)	2	2	(0.3)	3	3	(0.9)
Dermatitis	2	2	(0.3)	1	1	(0.2)	0	0	-
Contact Dermatitis	0	0	-	1	1	(0.2)	2	2	(0.6)
Acne (Flare)	1	1	(0.2)	2	2	(0.3)	0	0	-
Pruritus	0	0	-	1	1	(0.2)	0	0	-
Skin Discomfort	0	0	-	1	1	(0.2)	0	0	-
Erythema	0	0	-	1	1	(0.2)	0	0	-
Vesicular Rash	0	0	-	1	1	(0.2)	0	0	-
Cyst (face)	0	0	-	1	1	(0.2)	0	0	-
Herpes Simplex	0	0	-	1	1	(0.2)	0	0	-

(a) Excluded patients (86) from CR92142 since medical events have not been tabulated.

I:\GEL\SAFE\FDA.NDA

TABLE 2
OVERVIEW OF STUDIES WITH ADAPALENE GEL
(COMPLETED SINCE THE FILING OF NDA 20-380)

Study No.	Description	Treatment(s)	No. of Subjects *	Treatment Duration
CR92144	Cumulative Skin Irritation	Combination of Adapalene gel with each of the following: benzoyl peroxide, clindamycin phosphate or erythromycin	25	3 weeks
CR92140	Cumulative Skin Irritation	Adapalene gel Adapalene gel (different preservative)	25	3 weeks
CR92143	Phototoxicity Potential	Adapalene gel Tretinoin gel Isotretinoin gel Adapalene gel vehicle	12	1 day
CR92141	Photo-irritation Potential	Adapalene gel Tretinoin gel	12	15 days
CG.03.SPR.2005	Systemic Evaluation of adapalene in the stratum corneum	Adapalene gel	6	7 days
CG.03.SPR.2017	Cumulative Skin Irritation	Adapalene gel, 0.3% Adapalene gel vehicle	25	3 weeks
CR92142	Safety and Efficacy (acne patients)	Adapalene gel Isotretinoin gel	86	12 weeks

*Exposed to Adapalene Gel 0.1% unless otherwise indicated under *Treatment(s)*.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: November 30, 1990.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
OWEN/Galderma Laboratories, Inc.	March 19, 1993
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO *(Include Area Code)*
Post Office Box 6600 Fort Worth, Texas 76115	(817)551-8516
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued)
	20-338

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
ADAPALENE (USAN)	DIFFERIN™

CODE NAME *(If any)*	CHEMICAL NAME
CD 271 AL02866	6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Solution	Topical to the skin.	0.1% (1mg/ml)

PROPOSED INDICATIONS FOR USE

DIFFERIN™ Solution 0.1% (adapalene) is indicated for topical treatment of acne vulgaris.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

"Pre-NDA Submission of Chemistry, Manufacturing, and Controls Data"

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001 Expiration Date; November 30, 1990. See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT OWEN/GALDERMA LABORATORIES, INC.	DATE OF SUBMISSION December 14, 1992
ADDRESS *(Number, Street, City, State and Zip Code)* Post Office Box 6600 Fort Worth, Texas 76115	TELEPHONE NO. *(Include Area Code)* (817)551-8516 NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
ADAPALENE (USAN)	DIFFERIN ™

CODE NAME *(If any)*	CHEMICAL NAME
CD 271 AL02866	6-[3-(1-adamantyl)-4-methoxyphenyl]-2-Naphthoic acid

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Solution	Topical to the skin	0.1% (mg/mL)

PROPOSED INDICATIONS FOR USE

DEFFERIN™ Solution 0.1% (adapalene) is indicated for topical application in the treatment of acne vulgaris.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☒ PRESUBMISSION ☐ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

X	1. Index (Section Index to ITEMS 3, 4.a and 4.b)
	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
X	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. OTHER *(Specify)* Generic Drug Enforcement Act Certification

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Christine E. Shank Manager, Regulatory Affairs	Christine Shank	12/14/92

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO *(Include Area Code)*
Post Office Box 6600 Fort Worth, Texas 76115	(817)551-8516

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 20 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0001)
Washington, DC 20503

GALDERMA

ORIGINAL

NC

March 16, 1995

L. Ross Pierce, M.D.
Clinical Investigations Branch
Division of Scientific Investigations, HFD-344
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

MAR 17 1995
HFD-020
EVALUATION AND RESEARCH

RE: NDA 20-380
DIFFERIN™ (adapalene) Topical Gel, 0.1%

Dear Dr. Pierce:

Reference is made to your fax dated March 14, 1995 requesting information to assist in the audit of pivotal studies conducted with Differin™ (adapalene) Topical Gel, 0.1%.

Per your request please find enclosed the three items you highlighted as urgent (items 3,8 and 9 from your 15 item list). Additionally you will find a list and table of the studies (your item 2) which were identified as meeting the criteria of "adequate and well-controlled" and therefore considered "pivotal" by the applicant. It is unknown to us which studies were considered "pivotal" by the medical reviewer as the medical review has not been communicated to us.

It is anticipated that the information for the remaining 11 items will be sent to you by the end of next week.

Please contact me if you have any questions.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817) 263-2676
Facsimile: (817) 263-2667

copies: Archival (1) to NDA 20-380
Desk Copy (1) to Dr. Pierce (HFD-344)
Cover Letter Only - Faxed to Ms. R. Cook (HFD-540)

GALDERMA

ORIGINAL

NC

April 4, 1995

L. Ross Pierce, M.D.
Clinical Investigations Branch
Division of Scientific Investigations (HFD-344)
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

RE: NDA 20-380
DIFFERIN™ (adapalene) Topical Gel, 0.1%

Dear Dr. Pierce:

Reference is made to your fax dated March 14, 1995 requesting information to assist in the audit of pivotal studies conducted with Differin™ (adapalene) Topical Gel, 0.1%. Reference is also made to our submission of March 16, 1995 which provided you responses to Items 2,3,8 and 9 from your 15 item list.

Please find enclosed three volumes (plus an extra copy of Items 4 and 5) which contain responses to the remaining items you requested. All materials, except where noted, are copied from the NDA for Differin Topical Gel.

I have forwarded a copy of the "new" information to the NDA file. Previously submitted documents have not been duplicated but are incorporated by reference to the NDA page numbers.

Please advise if I can be of further assistance.

Sincerely,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817) 263-2676
Facsimile: (817) 263-2667

cc: Archival - New documents only (HFD-540)
Desk Copy - Dr. Pierce (HFD-344) 3 volumes
Cover Letter Only - faxed to Ms. R. Cook (HFD-540)

GALDERMA

DESK COPY

CERTIFIED MAIL # P 373 566 857
Return Receipt Requested

September 24, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-338
Adapalene Topical Solution, 0.1%

NDA 20-380
Adapalene Topical Gel, 0.1%

Dear Sir or Madam:

We acknowledge receipt on September 20, 1993, of a FAX from Ms. Rosemary Cook, FDA Project Manager, containing Chemistry Review comments relative to NDA 20-338. We further acknowledge that, in principle, some of the comments can also be considered relevant to NDA 20-380.

The applicant has reviewed these comments with management and personnel at DPT Laboratories, Inc., and agree that a full response can be submitted by October 29, 1993. We appreciate the opportunity to contact the reviewer, Mr. Timper, for clarification and/or assistance in understanding the comments as necessary.

Sincere regards,

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

GALDERMA LABORATORIES, INC.

SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

GALDERMA

CERTIFIED MAIL # P 378 566 858
Return Receipt Requested

DESK COPY

September 24, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%

Dear Sir or Madam:

Reference is made to a telephone call on September 17, 1993, from Ms. Rosemary Cook, FDA Project Manager, regarding inspection readiness of the facilities designated for manufacture of the proposed drug product, Adapalene Topical Gel, 0.1%.

Ms. Cook was advised that the applicant was unaware of any outstanding manufacturing or controls issues, and that the DPT Laboratories, Inc. facilities were considered fully operational and ready for inspection.

Sincere regards,

Christine Shank

Christine E. Shank
Manager, Regulatory Affairs

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05

GALDERMA LABORATORIES, INC.

SUITE 300 3000 ALTA MESA BLVD. P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

GALDERMA

NDA ORIG AMD

ORIGINAL BC

December 17, 1993

Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

DEC 2 - 1993

RE: NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%
Chemistry, Manufacturing and Controls

Dear Mr. Timper:

We are pleased to submit, herewith, an amendment to the NDA for Adapalene Topical Gel, 0.1% which addresses the raw material controls issues raised during the Adapalene Solution (NDA-338) pre-approval inspection at DPT Laboratories, Inc.

Volume 1 of this amendment describes the changes made in analytical procedures used by DPT Laboratories, Inc. for control of the drug substance and finished drug product. Please note we are incorporating, by reference, all relevant information on the drug substance from the October 29, 1993 and November 24, 1993 amendments to NDA 20-338. I hope this is satisfactory.

Volume 2 contains a complete and comprehensive resubmission of the SAMPLES and METHODS VALIDATION Package. The amended document incorporates all revisions described in Volume 1 and thus is representative of the controls currently used by DPT Laboratories, Inc. Two extra copies of Volume 2 are provided for submission to the FDA Analytical Laboratories.

This amendment establishes that all procedures, as presented, will be used by DPT Laboratories, Inc. for control of the drug substance and finished drug product.

Pursuant to 21 CFR 314.70 (a) and 314.71 (b) as amended by Final Rule published in the Federal Register September 8, 1993, the applicant makes the following certification:

GALDERMA LABORATORIES, INC.

SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331329, FORT WORTH, TX 76163 (817) 263-2600

A Field Copy of this amemdment, in its entirety, is provided to the FDA Dallas District Office, which is the home office for the applicant and the drug product manufacturer, DPT Laboratories, Inc., San Antonio, Texas.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone (817)263-2676
FAX (817)263-2667

DESK COPY: Ms. Rosemary Cook
HFD-520, Room 12B-05
(correspondence only)

GALDERMA

DUPLICATE

March 11, 1994

Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Jonathan Wilkin, M.D.
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-380/Amendment
Adapalene Topical Gel, 0.1%
Statistical Data

Dear Dr. Wilkin:

Reference is made to a request on March 7 (via telephone) from Dr. Srinivasan (HFD-713) for SAS datasets of specific parameters from clinical studies submitted in NDA 20-380.

Please find enclosed the requested statistical tables. A complete Desk Copy and two diskettes have been sent directly to Dr. Srinivasan.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs

DESK COPY: R. Srinivasan, Ph.D.
HFD-713, Room 15B-45 (includes 2 diskettes)

Ms. Rosemary Cook
HFD-540, Room 12B-05

GALDERMA

Orig
BC

May 1, 1995

Food and Drug Administration
Division of Topical Drug Products (HFD-540)
Center for Drug Evaluation and Research
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-380
Adapalene Topical Gel, 0.1%
Chemistry, Manufacturing and Controls Amendment

Dear Sir or Madame:

Reference is made to a telephone conference call with Ms. Rosemary Cook and Mr. Jim Timper, FDA representatives, and Mr. Raymon McElhaney and Ms. Christine Shank, sponsor representatives, on April 21, 1995.

Based on our understanding of the issues discussed, the following items are provided to correct all outstanding deficiencies regarding chemistry, manufacturing and controls for the drug substance, adapalene, and the drug product, DIFFERIN (adapalene) Topical Gel, 0.1%.

1. Addition of finished drug product test and specification for Viscosity.

2. Addition of finished drug product test and specification for Identity of adapalene by TLC.

3. Withdrawal of reprocessing provisions for the bulk drug product. A batch adjustment provision is retained which is a minor provision for addition of purified water to compensate for high values of adapalene and/or methylparaben.

4. Request for tentative 3 year (36 months) expiration dating based on real time room temperature data from stability studies conducted on the three validation batches produced at DPT Laboratories, Inc.

5. Adapalene drug substance process validation report from

Please note that the sponsor is able to provide a copy of the process validation report for Adapalene drug substance. In a letter to the FDA Drug Master File Staff dated April 24, 1995, Finorga advised that a revised DMF for

GALDERMA LABORATORIES, INC.
SUITE 300, 3000 ALTA MESA BLVD., P.O. BOX 331328, FORT WORTH, TX 76163 (817) 263-2600

adapalene has been submitted in addition to the process validation report. As the sponsor was not given a copy of the revised DMF, we can only request incorporation of this information in support of the NDA as previously authorized by To the best of our knowledge (per contacts with by Galderma the revised DMF incorporates all the relevant changes that resulted from responses to the FDA Form 483 inspection observations (NDA Amendments dated April 26, 1994; June 16, 1994 and November 10, 1994).

We sincerely appreciate Mr. Timper's advice, supportive concern and assistance towards a satisfactory resolution of the CMC issues. Please contact me if there are any questions.

Sincere regards,

Christine Shank

Christine Shank
Manager, Regulatory Affairs
Telephone: (817) 263-2676
Facsimile: (817) 263-2667

Field Copy Certification: A field copy of this amendment, in its entirety, is provided to the FDA Dallas District Office which is the home office for the applicant and the drug product manufacturer, DPT Laboratories, Inc., San Antonio, Texas. This certification is made pursuant to 21 CFR 314.60(c) of the regulations.

Christine Shank

Christine Shank, Manager Regulatory Affairs

cc: Archival
Review
Ms. Rosemary Cook (faxed copy of cover letter only)