HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DIFFERIN Lotion safely and effectively. See full prescribing information for DIFFERIN Lotion.

DIFFERIN® (adapalene) Lotion, 0.1%
For topical use
Initial U.S. Approval: 1996

----------INDICATIONS AND USAGE----------
DIFFERIN Lotion is a retinoid product indicated for the topical treatment of acne vulgaris in patients 12 years and older. (1)

----------DOSAGE AND ADMINISTRATION----------
Apply a thin film of DIFFERIN Lotion to the entire face and other affected areas of the skin once daily, after washing gently with a mild soapless cleanser. Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face. Avoid application to the areas of skin around eyes, lips and mucous membranes. (2)

DIFFERIN Lotion is for topical use only and not for oral, ophthalmic, or intravaginal use. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Lotion, 0.1% (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided. (5.1)
Erythema, scaling, dryness, and stinging/burning may occur with use of DIFFERIN Lotion. (5.2)

----------ADVERSE REACTIONS----------
Dry skin of mild to moderate severity was the most frequently reported (≥ 1%) treatment related adverse event. Erythema, scaling, dryness, burning/stinging were also seen during treatment. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
Concomitant use of topical products with a strong drying effect can increase skin irritation. Use with caution, especially in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN Lotion. (7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DIFFERIN Lotion is indicated for the topical treatment of acne vulgaris in patients 12 years and older.

2 DOSAGE AND ADMINISTRATION

Apply a thin film of DIFFERIN Lotion to the entire face and other affected areas of the skin once daily, after washing gently with a mild soapless cleanser. Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face. Avoid application to the areas of skin around eyes, lips and mucous membranes. DIFFERIN Lotion is for topical use only and not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Lotion, 0.1%. Each gram of the lotion contains 1 mg of adapalene in a white to off-white oil-in-water emulsion.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ultraviolet Light and Environmental Exposure

Exposure to sunlight, including sunlamps, should be avoided during the use of DIFFERIN Lotion. Patients with high levels of sun exposure and those with inherent sensitivity to sun should be warned to exercise caution. Use of sunscreen products and protective apparel (e.g. hat) are recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, may be irritating to patients under treatment with DIFFERIN Lotion.

5.2 Local Cutaneous Reactions

Signs and symptoms of local skin irritation (such as erythema, scaling, dryness, stinging/burning) may be experienced with use of DIFFERIN Lotion. These are most likely to occur during the first 2 weeks of treatment, are mostly mild to moderate in severity, and usually lessen with continued use of DIFFERIN Lotion. Depending upon the severity of these side effects, patients should be instructed to use a moisturizer, reduce the frequency of the application of DIFFERIN Lotion 0.1%, or discontinue use.

DIFFERIN Lotion should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with DIFFERIN Lotion. Avoid concomitant use of other potentially irritating topical products (abrasive soaps and cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes).

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

A total of 2141 subjects with acne vulgaris, 12 years and older, were treated once daily for 12 weeks. Of these, 1068 were exposed to DIFFERIN Lotion during the clinical trials. A total of 1057 subjects completed at least one post treatment evaluation. Related adverse reactions that were reported in at least 1% of subjects treated with DIFFERIN Lotion or with the Vehicle Lotion are presented in Table 1. The majority of cases were transient, mild to moderate in severity and were managed with moisturizers.

Table 1: Adverse Reactions Reported in Clinical Trials by At Least 1% of Subjects

System Organ Class/ Preferred Term	Adapalene Lotion 0.1% N = 1068	Vehicle Lotion N = 1073
Subjects with Related AR(s)	10.2%	4.6%
Dry Skin	7.7%	3.0%
Skin irritation	1.5%	0.7%
Skin burning/skin discomfort	0.9%	0.0%
Sunburn	0.6%	0.6%

Local tolerability evaluations, presented in Table 2, were conducted at each study visit in clinical trials. Erythema, scaling, dryness, burning/stinging were assessed:

Table 2: Incidence of Local Cutaneous Irritation, for Subjects Whose Irritation Score was Higher than at Baseline, in Controlled Clinical Trials Adverse Reactions

(DIFFERIN Lotion Group N = 1057*)

Combined Trial 1 and Trial 2	Maximum Severity During Treatment (N = 1057)			Week 12 Treatment Severity (N = 950)		
Local Cutaneous Irritation (skin irritation)	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	21.8%	8.0%	0.2%	7.9%	2.6%	0.2%

Scaling	25.3%	6.5%	0.1%	5.3%	1.1%	0%
Dryness	36.1%	7.3%	0.3%	7.6%	2.0%	0%
Stinging/burning	22.1%	7.0%	0.9%	4.6%	1.0%	0.4%

* Data from 11 subjects with missing data are not included.

Local tolerability scores for erythema, scaling, dryness, burning/stinging rose during the first two weeks of treatment and generally decreased thereafter.

In an open label postmarketing pharmacokinetic trial of 13 adolescent subjects, the adverse event of pruritus was reported in 8 out of 13 subjects.

7 DRUG INTERACTIONS

7.1 Concomitant Topical Medications

Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. Caution should be exercised in using preparation containing sulfur, resorcinol or salicylic acid in combination with DIFFERIN Lotion.

No formal drug-drug interaction studies were conducted with DIFFERIN Lotion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with DIFFERIN Lotion. Therefore, DIFFERIN Lotion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with DIFFERIN Lotion. Furthermore, such studies are not always predictive of human response.

Human Data

In clinical trials involving DIFFERIN Lotion, 0.1% in the treatment of acne vulgaris, women of childbearing potential initiated treatment only after a negative pregnancy test. Two women became pregnant while using DIFFERIN Lotion, 0.1%. One patient delivered a healthy full term baby and the other patient electively terminated her pregnancy.

Animal Data

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m^2/day) the maximum recommended human dose (MRHD) of 2 grams of DIFFERIN Lotion. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of $\geq$ 25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m^2) the MRHD] exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

Systemic exposure (AUC $_{0\text{-}24h}$) to adapalene at topical doses (6.0 mg/kg/day) in rats represented 101 times the exposure to adapalene in patients with acne treated with DIFFERIN Lotion applied to the face, chest and back (2 grams applied to 1000 cm² of acne-involved skin).

8.3 Nursing Mothers

It is not known whether adapalene is excreted in human milk following use of DIFFERIN Lotion. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Lotion is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of DIFFERIN Lotion in pediatric patients under the age of 12 have not been established.

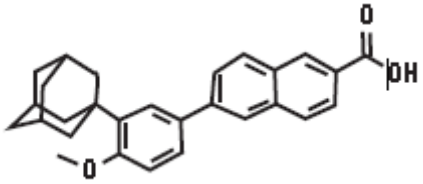
8.5 Geriatric Use

Clinical studies of DIFFERIN Lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

DIFFERIN (adapalene) Lotion, 0.1% for topical use, contains adapalene in a white to off-white oil-in-water emulsion.

Adapalene is a naphthoic acid derivative with retinoid-like properties. The chemical name for adapalene is (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid). Adapalene has the following structural formula:



Adapalene:

Molecular formula: $C_{28}H_{28}O_3$ Molecular weight: 412.5

Each gram of DIFFERIN Lotion contains 1 mg of adapalene. The lotion also contains the following inactive ingredients: carbomer 941, disodium edetate, medium chain triglycerides, methylparaben, phenoxyethanol, poloxamer 124, polyoxyl-6-polyoxyl-32 palmitostearate, PPG-12/SMDI copolymer, propylene glycol, propylparaben, purified water, sodium hydroxide, and stearyl alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adapalene binds to specific retinoic acid nuclear receptors but does not bind to cytosolic receptor protein. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes. However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne is unknown.

12.2 Pharmacodynamics

Pharmacodynamics of DIFFERIN Lotion is unknown.

12.3 Pharmacokinetics

Systemic exposure of adapalene following a topical application of DIFFERIN Lotion was studied in two pharmacokinetic (PK) clinical trials. The first trial was conducted in 14 adult subjects 18 to 29 years of age with severe acne and the second trial was conducted in 13 adolescent subjects 12 to 17 years of age with moderate to severe acne.

In each trial, subjects were treated with 2 g of DIFFERIN Lotion applied once daily to approximately 1000 cm² of acne involved skin for 28 days (adolescent subjects) or 30 days (adult subjects). Serial plasma samples were collected at 24 or 72 hours following application on days 1, 15 and 28/30.

Daily topical application of DIFFERIN Lotion resulted in low systemic exposure to adapalene in the two populations (adult and adolescent subjects).

In the adult population, all plasma concentrations in 12 out of 14 subjects were below the limit of quantification (LOQ=0.1 ng/mL). One subject had one sample above LOQ at day 30 and the other subject had four plasma samples above LOQ on both days 1 and 15, which ranged from 0.102 and 0.131 ng/mL.

In the adolescent population, plasma concentrations were quantifiable (>0.1 ng/mL) in five subjects. On Day 28, the mean C_{max} was 0.128 ± 0.049 ng/mL (range: <0.100 to 0.244 ng/mL) and the mean of $AUC_{0\text{-}24hr}$ was 3.07 ± 1.21 ng.hr/mL (range: 1.86 to 4.93 ng.hr/mL). Adapalene plasma concentrations in all subjects were below the limit of quantification (<0.1 ng/mL) 48 hours after the last application on Day 28.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity and impairment of fertility studies were conducted with DIFFERIN Lotion. Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m^2/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of DIFFERIN Lotion. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed. No photocarcinogenicity studies were conducted with adapalene. However, 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 sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources. Adapalene did not exhibit mutagenic or genotoxic effects *in vitro* (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or *in vivo* (mouse micronucleus test). In rat oral studies, 20 mg adapalene/kg/day (120 mg/m^2/day; 98 times the MRHD based on mg/m^2/day comparison) did not affect the reproductive performance and fertility of F_0 males and females, or growth, development and reproductive function of F_1 offspring.

14 CLINICAL STUDIES

The safety and efficacy of DIFFERIN Lotion applied once daily for the treatment of acne vulgaris were assessed in two 12-week, multicenter, controlled clinical trials of similar design, comparing DIFFERIN Lotion to the lotion vehicle in acne subjects.

In Trial 1, 1075 subjects were randomized to DIFFERIN Lotion or vehicle. The median age of these subjects was 16.7 years old and 53.1% were females. At baseline subjects had between 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions. The majority of subjects (91.0%) had a baseline IGA score of 'Moderate'.

In Trial 2, 1066 subjects were randomized to DIFFERIN Lotion or vehicle. The median age of subjects was 16.7 years old and 53.7% were females. At baseline subjects had the same inclusion criteria as in Trial 1 and 95.7% of subjects had a baseline IGA score of 'Moderate'.

The outcome of the two trials is presented in Table 3.

Table 3: Clinical Trial Primary Efficacy Results at Week 12

Trial 1		
	DIFFERIN Lotion (N = 533)	Vehicle Lotion (N = 542)
IGA Success	140 (26.3%)	94 (17.3%)
Total Lesions: Mean Absolute (Percent) Change	37.9 (51.5%)	26.7 (37.1%)
Inflammatory Lesions: Mean Absolute (Percent) Change	14.7 (54.9%)	10.6 (40.3%)
Non-inflammatory Lesions: Mean Absolute (Percent) Change	23.2 (49.6%)	16.1 (35.7%)

Trial 2		
	DIFFERIN Lotion (N = 535)	Vehicle Lotion (N = 531)
IGA Success	129 (24.1%)	87 (16.4%)

Total Lesions: Mean Absolute (Percent) Change	32.4 (44.6%)	23.4 (32.8%)
Inflammatory Lesions: Mean Absolute (Percent) Change	12.7 (46.0%)	10.2 (36.9%)
Non-inflammatory Lesions: Mean Absolute (Percent) Change	19.6 (43.1%)	13.1 (30.2%)

16 HOW SUPPLIED/STORAGE AND HANDLING

DIFFERIN (adapalene) Lotion, 0.1%, is a white to off-white liquid packaged in a 2 oz (59 mL) bottle which is equipped with a lotion dispensing pump.
DIFFERIN Lotion is supplied as follows:
2 oz bottle pump **NDC 0299-5912-02**

Storage and handling

- Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). [see USP Controlled Room Temperature]
- Do not freeze.
- Do not refrigerate.
- Protect from light.
- Keep out of reach of children.
- Keep away from heat.
- Keep bottle tightly closed.

17 PATIENT COUNSELING INFORMATION

- Apply a thin film of DIFFERIN Lotion to the affected areas of the skin once daily, after washing gently with a mild soapless cleanser. Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face. Avoid application to the areas of skin around eyes, lips and mucous membranes. DIFFERIN Lotion may cause irritation such as erythema, scaling, dryness, stinging or burning.
- Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply DIFFERIN Lotion to the entire face or other acne affected areas as a thin layer, avoiding the eyes, lips and mucous membranes.
- Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis and eye irritation.
- Patients should be advised not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.
- Advise patients to minimize exposure to sunlight including sunlamps. Recommend the use of sunscreen products and protective apparel (e.g., hat) when exposure cannot be avoided.
- Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.
- This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.
- Wax depilation should not be performed on treated skin due to the potential for skin erosions.
- This product is for external use only.

Marketed by:
GALDERMA LABORATORIES, L.P., Fort Worth, Texas 76177 USA

Manufactured by:
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