DIFFERIN - adapalene lotion
Galderma Laboratories, L.P.

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, 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 once daily, after washing gently with a mild soapless cleanser. (2)
- Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face and other affected areas of the skin. (2)
- Avoid application to the areas of skin around eyes, lips and mucous membranes. (2)
- For topical use only and not for oral, ophthalmic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Lotion, 0.1% in 2 oz bottle with pump. (3)

CONTRAINDICATIONS

Contraindicated in patients with known hypersensitivity to adapalene or any excipient of DIFFERIN Lotion. (4)

WARNINGS AND PRECAUTIONS

- *Allergic/ Hypersensitivity Reactions:* Allergy/hypersensitivity reactions include anaphylaxis, angioedema, urticaria, and pruritis. Discontinue DIFFERIN Lotion in the event of an allergic/hypersensitivity reaction. (5.1)
- *Ultraviolet Light and Environmental Exposure:* Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided. (5.2)
- *Local Cutaneous reactions:* Erythema, scaling, dryness, and stinging/burning may occur with use of DIFFERIN Lotion. Avoid application of DIFFERIN Lotion to cuts, abrasions, eczematous or sunburned skin. 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). (5.3)

ADVERSE REACTIONS

The most common adverse reactions reported (≥ 1%) are dry skin and skin irritation. (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*
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2022

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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

Wash affected areas gently with a mild soapless cleanser.

Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) and apply a thin film to the entire face and other affected areas of the skin once daily.

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. DIFFERIN Lotion is available in 2 oz bottle with pump.

4 CONTRAINDICATIONS

DIFFERIN Lotion is contraindicated in patients who have known hypersensitivity to adapalene or any excipient of DIFFERIN Lotion [*see WARNINGS AND PRECAUTIONS (5.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Allergic/ Hypersensitivity Reactions

Anaphylaxis, angioedema, urticaria, face edema, eyelid edema, lip swelling, and pruritus that sometimes required medical treatment have been reported during postmarketing use of adapalene. Advise a patient to stop using DIFFERIN Lotion and seek medical attention if experiencing allergic or anaphylactoid/anaphylactic reactions during treatment.

5.2 Ultraviolet Light and Environmental Exposure

Avoid exposure to sunlight, including sunlamps, 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..

5.3 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 or discontinue use.

Avoid application of DIFFERIN Lotion 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 Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials 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 reaction of pruritus was reported in 8 out of 13 subjects.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of adapalene:

Immune system disorders: angioedema, face edema, lip swelling

Skin disorders: application site pain

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Available data from clinical trials with DIFFERIN Lotion use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of adapalene to pregnant rats and rabbits during organogenesis at dose exposures 122 and 243 times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 2 g resulted in fetal skeletal and visceral malformations (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data
Animal Data
No malformations were observed in rats treated with oral adapalene doses of 0.15 to 5.0 mg/kg/day, up to 24 times the MRHD based on a mg/m2 comparison. However, malformations were observed in rats and rabbits when treated with oral doses of ≥ 25 mg/kg/day adapalene (122 and 243 times the MRHD, respectively, based on a mg/m^2 comparison). Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits.

Dermal adapalene embryofetal development studies in rats and rabbits at doses up to 6.0 mg/kg/day (29 and 58 times the MRHD, respectively, based on a mg/m^2 comparison) exhibited no fetotoxicity and only minimal increases in skeletal variations (supernumerary ribs in both species and delayed ossification in rabbits).

8.2 Lactation

Risk Summary
There are no data on the presence of topical adapalene lotion or its metabolite in human

milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, adapalene is present in rat milk with oral administration of the drug. When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is possible that topical administration of large amounts of adapalene could result in sufficient systemic absorption to produce detectable quantities in human milk (*see Clinical Considerations*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DIFFERIN Lotion and any potential adverse effects on the breastfed child from DIFFERIN Lotion or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breastmilk, use DIFFERIN Lotion on the smallest area of skin and for the shortest duration possible while breastfeeding. Avoid application of DIFFERIN Lotion to areas with increased risk for potential ingestion by or ocular exposure to the breastfeeding child.

8.4 Pediatric Use

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

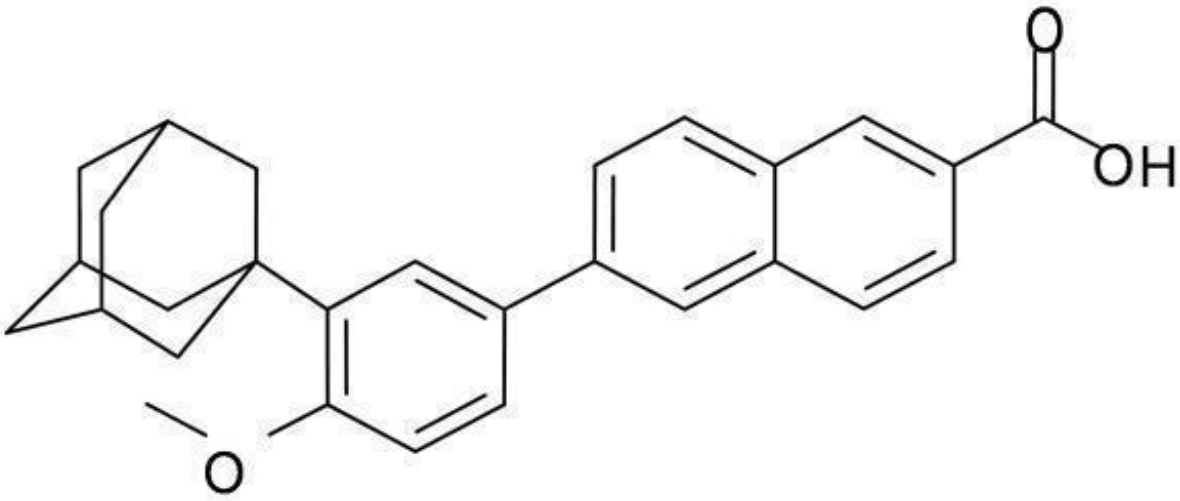
8.5 Geriatric Use

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, 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)-4methoxyphenyl]- 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, PPG12/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 cm^2 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, genotoxicity, or impairment of fertility studies were conducted with DIFFERIN Lotion.

Carcinogenicity studies with adapalene were conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m^2/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). The highest dose levels are 9.8 (mice) and 7.4 (rats) times the MRHD based on a mg/m^2 comparison. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed.

Adapalene was not mutagenic or genotoxic in vitro (Ames test, Chinese hamster ovary cell assay, or mouse lymphoma TK assay) or in vivo (mouse micronucleus test). In rat oral studies, 20 mg/kg/day adapalene (97 times the MRHD based on a mg/m^2 comparison) did not affect the reproductive performance and fertility of F_0 males and females or the growth, development, or 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%)	95 (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

Patients using DIFFERIN Lotion should receive the following information and instructions:

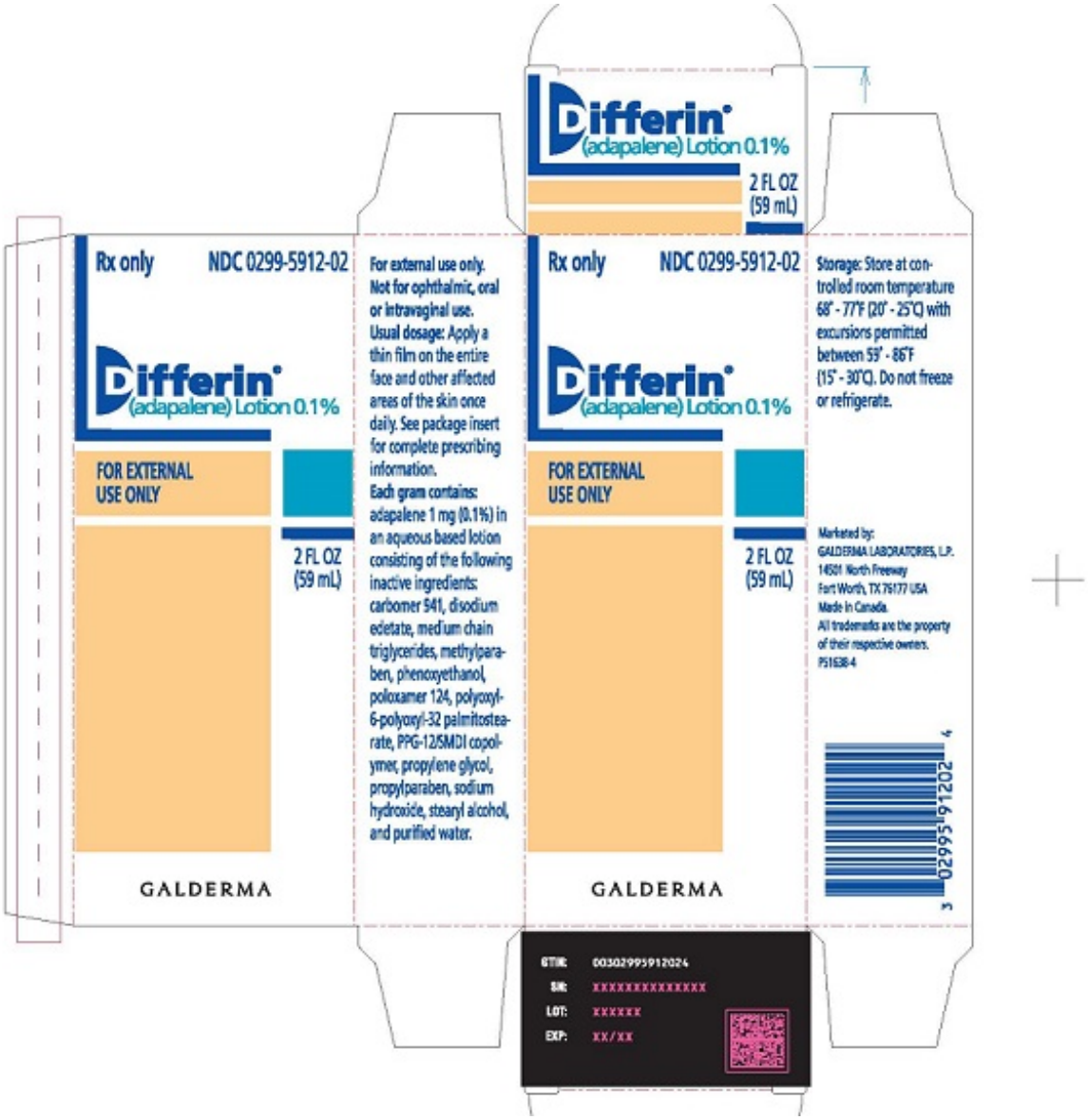
- Wash affected areas gently with a mild soapless cleanser.
- Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) and apply a thin film to the entire face and other affected areas of the skin once daily.
- Avoid application to the areas of skin around eyes, lips and mucous membranes.
- Do not apply to cuts, abrasions, eczematous, or sunburned skin.
- Wax depilation should not be performed on treated skin due to the potential for skin erosions.
- DIFFERIN Lotion may cause irritation such as erythema, scaling, dryness, stinging or burning. 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 product is for external use only.
- Contact the doctor if skin rash, pruritus, hives, chest pain, edema, and shortness of breath occurs, as these may be signs of allergy or hypersensitivity.
- Lactation: Use DIFFERIN Lotion on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply DIFFERIN Lotion to areas with increased risk for potential ingestion by or ocular exposure to the breastfeeding child. [See *Use in Specific Populations, Lactation (8.2)*]

Marketed by:
GALDERMA LABORATORIES, L.P., Dallas, Texas 75201 USA

Made in Canada.
All trademarks are property of their respective owners.
P51503-3

PACKAGE LABEL - 2 FL OZ CARTON



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Rx Only

NDC 0299-5912-02

Differin®
(adapalene) Lotion 0.1%

For External
Use Only

2 FL OZ
(59 mL)

GALDERMA

For external use only.

Not for ophthalmic, oral or intravaginal use.

Usual dosage: Apply a thin film on the entire face and other affected areas of the skin once daily. See package insert for complete prescribing information.

Each gram contains: adapalene 1 mg (0.1%) in an aqueous based lotion consisting of 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, sodium hydroxide, stearyl alcohol, and purified water.

Storage: Store at controlled room temperature 68° - 77°F (20° - 25°C) with excursions permitted between 59° - 86°F (15° - 30°C). Do not freeze or refrigerate.

Marketed by:
GALDERMA LABORATORIES, L.P.
14501 North Freeway
Fort Worth, Texas 76177 USA
Made in Canada.

P51638-4

DIFFERIN
adapalene lotion

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0299-5912
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Adapalene (UNII: 1L4806J2QF) (Adapalene - UNII:1L4806J2QF)	Adapalene	0.1 g in 100 mL

Inactive Ingredients

Ingredient Name	Strength
Carbomer Homopolymer Type A (UNII: F68VH75CJC)	
Edetate Disodium (UNII: 7FLD91C86K)	
Medium-chain Triglycerides (UNII: C9H2L21V7U)	
Methylparaben (UNII: A2I8C7HI9T)	
Phenoxyethanol (UNII: HIE492ZZ3T)	
Poloxamer 124 (UNII: 1S66E28KXA)	
POLYETHYLENE GLYCOL 300 (UNII: 5655G9Y8AQ)	
POLYETHYLENE GLYCOL 1500 (UNII: 1212Z7S33A)	
Propylene Glycol (UNII: 6DC9Q167V3)	
Propylparaben (UNII: Z8IX2SC1OH)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Stearyl Alcohol (UNII: 2KR89I4H1Y)	
Water (UNII: 059QF0KO0R)	

Product Characteristics

Color	white (white to off-white)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0299-5912-02	1 in 1 CARTON	04/27/2010	
1		59 mL in 1 BOTTLE, PUMP; Type 0: Not a Combination Product		
2	NDC:0299-5912-01	15 mL in 1 BOTTLE; Type 0: Not a Combination Product	04/27/2010	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022502	03/31/2010	

Labeler - Galderma Laboratories, L.P. (047350186)

Establishment

Name	Address	ID/FEI	Business Operations
G Production Inc.		251676961	manufacture(0299-5912)

Revised: 8/2022

Galderma Laboratories, L.P.