

PRODUCT MONOGRAPH

PrDIFFERIN®

adapalene topical cream

0.1% w/w

adapalene topical gel

0.1% w/w

adapalene topical lotion

0.1% w/w

PrDIFFERIN XP®

adapalene topical gel

0.3% w/w

Acne Therapy

GALDERMA CANADA INC.
55 Commerce Valley Dr. W.
4th Floor
Thornhill, Ontario L3T 7V9

Control No: 219933

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Pr DIFFERIN®
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 0.1% w/w
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 0.3% w/w

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
topical	cream 0.1% w/w	None
	gel 0.1%, 0.3% w/w	None
	lotion 0.1% w/w	None
		<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

DIFFERIN (adapalene) topical cream, gel and lotion, and DIFFERIN XP (adapalene) topical gel are indicated for:

- Topical treatment of *acne vulgaris* in patients 12 years of age and older.

Geriatrics (> 65 years of age):

Safety and effectiveness in geriatric patients aged 65 years and above have not been established.

Pediatrics (< 12 years of age):

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

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

Patients with eczema or seborrheic dermatitis.

Pregnancy

Women planning a pregnancy.

WARNINGS AND PRECAUTIONS

General

For external use only. Avoid contact with the eyes, lips, angles of the nose, mucous membranes and open wounds. Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus are associated with the topical application of retinoids and can also be expected with the use of DIFFERIN (adapalene) topical cream, gel or lotion, and with DIFFERIN XP (adapalene) topical gel. These treatment-related effects generally occur during the first two to four weeks of therapy and usually resolve as the skin undergoes adjustment with continued use. Depending on the degree of the side effects, patients can be directed to use a moisturizer, use the medication less frequently or temporarily discontinue use until the symptoms subside or to discontinue use altogether (see DOSAGE AND ADMINISTRATION).

As with any retinoid, exposure to excessive sunlight, including sunlamps, should be avoided while using the preparation, or a suitably effective sunscreen product and protective clothing over the 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. As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with adapalene.

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).

Patients should be advised to use non-comedogenic cosmetics. Colour cosmetics such as blushers and powders are acceptable, however, make-up cosmetics should be water based only. Cosmetics must be removed by thorough cleansing before the area is treated.

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Special Populations

Pregnant Women: Orally administered retinoids have been associated with congenital abnormalities. *Topical adapalene is contraindicated in pregnant women and women planning a pregnancy because of the possibility of an increased systemic exposure due to various factors (e.g. damaged skin barrier, excessive use).*

There have been rare reports of birth defects among babies born to women exposed to topical retinoids during pregnancy. However, there are no well controlled prospective studies of the use of topical retinoids, including adapalene, in pregnant women. A retrospective study of mothers exposed to topical tretinoin during the first trimester of pregnancy found no increase in the incidence of birth defects. If the patient becomes pregnant while using these drugs, treatment should be discontinued.

Adapalene administered orally at doses of ≥ 25 mg/kg/day (38 times the Maximum Recommended Human Dose [MRHD] based on mg/m² comparisons for rats or 65 times MRHD for rabbits) has been shown to be teratogenic. No teratogenic effects were seen in rats at oral doses of up to 5.0 mg/kg/day adapalene (7.6 times the MRHD). Cutaneous teratology studies in rats and rabbits at doses of 0.6 (0.03 %), 2.0 (0.1 %) and 6.0 (0.3 %) mg/kg/day (17 times the MRHD for rats or 32 times the MRHD for rabbits) exhibited no teratogenicity. At 2 mg/kg/day (0.1% adapalene gel), no adverse events were observed in rabbits and only a marginal increase in the incidence of additional lumbar ribs was observed in rats. However, at 6 mg/kg/day (0.3% adapalene gel), in addition to the recorded increase in foetal rib numbers in the rat and rabbit, there were also other skeletal anomalies in both species (see TOXICOLOGY). There are no adequate and well-controlled studies in pregnant women.

Nursing Women: It is not known whether this drug is excreted in human milk. Animal pharmacology studies indicate that adapalene is excreted in milk at levels lower than plasma levels. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN topical cream, gel or lotion, or DIFFERIN XP topical gel is administered to a nursing mother. To avoid contact exposure of the infant, application of DIFFERIN and DIFFERIN XP to the chest should be avoided when used during breast-feeding.

Pediatrics (12-16 years of age): No specific monitoring or hazards are associated with the use of the product in pediatric patients between the ages of 12 and 16 years. Safety and effectiveness in children below the age of 12 have not been established.

Geriatrics (> 65 years of age): Safety and effectiveness in geriatric patients age 65 and above have not been established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Treatment-related adverse reactions typically associated with use of DIFFERIN and DIFFERIN XP include mild to moderate application site reactions, such as skin irritation characterized by

scaling, dryness, erythema, burning and stinging. DIFFERIN XP results in a slightly greater incidence of these events, as would be expected with the higher concentration of adapalene. These reactions usually occur early in the treatment, and tend to resolve after 2 to 4 weeks of therapy (see WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

DIFFERIN (adapalene) Topical Cream or Topical Gel:

In clinical trials with DIFFERIN topical gel and cream 0.1%, 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. Contact allergy to topical adapalene was not reported during clinical trials. To date, all adverse effects of DIFFERIN topical cream or gel 0.1% have been reversible upon discontinuation of therapy.

DIFFERIN Topical Lotion:

During two multicentre, active- and vehicle-controlled, Phase III clinical trials, patients with acne vulgaris, 12 years and older, were treated with DIFFERIN Lotion or its vehicle once daily for 12 weeks. A total of 1068 patients were exposed to DIFFERIN Lotion in these trials. In general, most of the signs and symptoms of cutaneous irritation (erythema, scaling, dryness, and/or burning/stinging) were either mild or moderate in severity, and occurred primarily during the first two weeks of treatment, and decreased thereafter. The majority of cases of local irritation were managed with moisturizers.

DIFFERIN XP (adapalene) Topical Gel:

In a multi-centre, placebo- and active-controlled Phase III clinical trial, signs and symptoms of local cutaneous irritation were monitored in 258 adult acne patients who used DIFFERIN XP topical gel 0.3% once daily for 12 weeks. Of the patients who experienced cutaneous irritation (erythema, scaling, dryness, and/or burning/stinging), the majority of cases were mild to moderate in severity, occurred in the first week of treatment, and decreased thereafter.

In a one-year, open-label safety study of 551 patients with acne vulgaris who used DIFFERIN XP, the pattern of adverse events was similar to the 12-week controlled study. The percentage of subjects who experienced cutaneous irritation (scaling, erythema, dryness, and/or stinging/burning) greater than baseline was highest after one week of treatment and decreased thereafter, continuing to decrease during the one-year treatment period.

Table 1: Related Adverse Drug Reactions^a From Open, and Vehicle- and Active-Controlled Studies

	DIFFERIN XP adapalene gel 0.3% n= 1087 (%)	DIFFERIN adapalene gel 0.1% n=1463 (%)	DIFFERIN adapalene cream 0.1% n=311 (%)	DIFFERIN adapalene lotion 0.1% n=1068 (%)	Gel Vehicle n=134 (%)	Lotion Vehicle n=1073 (%)
Total No. (%) of Subjects with Related ¹ Adverse Drug Reaction(s)	267 (24.6%)	153 (10.5%)	16 (5.1%)	109 (10.2%)	6 (4.5%)	49 (4.6%)
Skin and Appendages	263 (24.2%)	164 (11.2%)	17 (5.5%)	109 (10.2%)	6 (4.5%)	48 (4.5%)
Skin dry	117 (10.8%)	58 (4.0%)	1 (0.3%)	79 (7.4%)	2 (1.5%)	32 (3.0%)
Erythema	27 (2.5%)	18 (1.2%)	0 (0%)	2 (0.2%)	0 (0%)	0 (0.0%)
Skin discomfort	70 (6.4%)	40 (2.7%)	1 (0.3%)	5 (0.5%)	0 (0%)	0 (0.0%)
Desquamation	28 (2.6%)	9 (0.6%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0.0%)
Pruritus	18 (1.7%)	13 (0.9%)	0 (0%)	5 (0.5%)	0 (0%)	5 (0.5%)
Sunburn	21 (1.9%)	13 (0.9%)	3 (1.0%)	2 (0.2%)	2 (1.5%)	1 (0.1%)
Irritant dermatitis	59 (5.4%)	33 (2.3%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0.0%)
Skin irritation	0 (0%)	4 (0.4%)	5 (1.6%)	8 (0.7%)	0 (0%)	7 (0.7%)

¹ Related = Possibly, probably, or definitely related

^a Adverse drug reactions do not include known local adverse events (local tolerability) of retinoids

The proportion of subjects with adverse events was generally higher for the DIFFERIN XP group compared to the adapalene gel 0.1% group, as was expected with the higher concentration. Almost all related adverse events were in the Skin and Appendages body system and most were mild to moderate in severity.

In controlled clinical trials for DIFFERIN Gel or Cream, 0.1%, local cutaneous irritation in acne patients was monitored. Patients commonly experienced cutaneous irritation (erythema, scaling, dryness, pruritis, and/or burning/stinging); the majority of cases were mild to moderate in severity.

In a controlled clinical trial for DIFFERIN Gel, 0.3%, local cutaneous irritation in acne patients was monitored. Patients very commonly experienced cutaneous irritation (erythema, scaling, dryness, and/or burning/stinging), the majority of cases were mild to moderate in severity, occurred early in treatment and decreased thereafter.

In controlled clinical trials for DIFFERIN Lotion, 0.1%, the incidence of local cutaneous irritation in acne patients was monitored and the data is provided in the following table:

Table 2: Incidence of Local Cutaneous Irritation - Emergent Signs and Symptoms for Adapalene Lotion in RD.06.SPR.18113 and RD.06.SPR.18114 (Combined)

Combined Studies	Maximum Severity During Treatment (N=1057)			End of Treatment (12 Weeks) Severity (N=950)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Local Cutaneous Irritation (skin irritation)						
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%

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following less common events have been designated as related (possibly, probably, definitely) to treatment with DIFFERIN AND DIFFERIN XP, considering all patients in the clinical trials in *acne vulgaris*:

Skin and Appendages: Eczema, contact dermatitis, atopic dermatitis, skin edema, dermatitis, acne, worsening of treated disease, urticaria, skin discolouration, seborrhea, herpes simplex, vesicular rash, eyelid edema, burning/stinging, pityriasis alba, erythematous rash, skin exfoliation

Body as a Whole: Pain, facial edema

Special Senses: Eye pain, keratoconjunctivitis

Abnormal Haematology and Clinical Chemistry: No significant abnormal values were observed in the short term controlled studies or the long term safety study.

Post-Market Adverse Drug Reactions

Skin and Appendages: allergic dermatitis (allergic contact dermatitis), pain of skin, skin swelling

Eye Disorders: eyelid irritation, eyelid erythema, eyelid pruritus, eyelid swelling.

The following isolated (one report each) serious, unexpected adverse events have been designated as probably/possibly related to treatment with an adapalene topical formulation: Papilloedema, hepatitis/cholectasis, convulsions, foetal disorders.

DRUG INTERACTIONS

Overview

There are no known interactions with other medications which are likely to be used topically and concurrently with DIFFERIN (adapalene) topical cream, gel or lotion, or with DIFFERIN XP (adapalene) topical gel. Absorption of adapalene through human skin is low, and therefore interaction with systemic medications is unlikely.

Drug-Drug Interactions

As DIFFERIN and DIFFERIN XP have the potential for local irritation, it is possible that concomitant use of abrasive cleansers, strong drying agents, or irritant products may produce additive irritant effects. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN topical cream, gel or lotion, or with DIFFERIN XP. If these preparations have been used, it is advisable not to start therapy with DIFFERIN until the effects of such preparations have subsided.

Other cutaneous anti-acne treatments (e.g., erythromycin topical solution, clindamycin phosphate topical solution 1% or benzoyl peroxide products in concentrations up to 10%) may be used in the morning when DIFFERIN topical cream, gel or lotion, or DIFFERIN XP is used at night.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Tests

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

DIFFERIN (adapalene) topical cream, gel and lotion, or DIFFERIN XP (adapalene) topical gel should be applied to the affected areas of the face, chest and back once a day before retiring and after washing. A small amount should be applied to provide a thin film, avoiding eyes, lips and mucous membranes. Ensure that the affected areas are dry before application.

DIFFERIN products should not come into contact with the eyes, mouth, angles of the nose or mucous membranes. If product enters the eye, wash immediately with warm water. This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.

Discontinue treatment if a severe local inflammatory response is experienced. Reinstigate therapy when the reaction has subsided, initially applying the preparation less frequently. Once daily application may be resumed if it is judged that the patient is able to tolerate the treatment.

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 topical gel has been demonstrated over a six-month period of treatment. Cutaneous safety of DIFFERIN XP topical gel has been demonstrated over a 12-month period of treatment.

Missed Dose

Dosing should continue as per usual the following evening, and the usual amount should be applied.

OVERDOSAGE

DIFFERIN (adapalene) topical cream, gel and lotion, and DIFFERIN XP (adapalene) topical gel are 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 adapalene topical gel, 0.1% in mice and rats is greater than 10 mL/kg (10 mg/kg). Inadvertent oral ingestion of adapalene may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A including teratogenesis in women of childbearing years. Therefore, in such cases, pregnancy testing should be carried out in women of childbearing years. In the event of accidental ingestion of the product, unless the amount accidentally ingested is small, an appropriate method of gastric emptying might be considered.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a potent modulator of cellular differentiation, keratinization and inflammatory processes all of which represent important features in the pathology of *acne vulgaris*. Mechanistically, adapalene binds to specific retinoic 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.

Pharmacodynamics

Studies in acne patients provide clinical evidence that topical adapalene is effective in reducing the noninflammatory acne lesions (open and closed comedones). Adapalene inhibits the chemotactic (directional) and chemokinetic (random) responses of human polymorphonuclear leucocytes in *in vitro* assay models; it also inhibits the metabolism of arachidonic acid, by lipoxidation, to inflammatory mediators. This profile suggests that the cell mediated inflammatory component of acne is modified by adapalene. Studies in human patients provide clinical evidence that topical adapalene is effective in reducing the inflammatory components of acne (i.e., papules and pustules).

Pharmacokinetics

Table 3: Summary of Adapalene's Pharmacokinetic Parameters in Adult Patients with *Acne vulgaris* Following Application of 0.3% Gel

	C_{max}	t_2 (h)	AUC ₀₋₂₄	Clearance
Repeated dose mean	0.553 ± 0.466 ng/mL ^a	13 - 16 ^b	8.94 ± 8.99 ng.hr/mL ^c	Within 72 hours

^a Derived from 15/16 subjects

^b Derived from 7/16 subjects

^c Derived from 14/16 subjects

Absorption: Absorption of adapalene through human skin is low. No quantifiable levels of parent substance have been found in the plasma of patients following chronic adapalene gel 0.1% application in controlled clinical trials (limit of quantification = 0.25 ng/mL). In adult patients with *acne vulgaris* who received daily applications of 0.3% gel for 10 days, the mean AUC_(0-24h) on Day 10 was 8.94 ng.h/mL (SD: 8.99) and the mean C_{max} was 0.553 ng/mL (SD: 0.466). The C_{max} ranged from < 0.1 to 2 ng/mL and the maximum AUC_(0-24h) value obtained was 36.1 ng.h/mL. The terminal apparent half-life ranged from 13 to 16 hours, thereby indicating that a pharmacokinetic steady-state was reached before Day 10.

Systemic exposure of adapalene following a topical application of adapalene lotion 0.1% was studied in one clinical study. Fourteen adult subjects with severe acne were treated with 2 g of adapalene lotion once daily for 30 days to approximately 1000 cm² of acne involved skin. Serial plasma samples were collected for 24 or 72 hours following application on days 1, 15 and 30. All plasma concentrations for 12 out of 14 patients were below the limit of quantification (LOQ=0.1 ng/mL). One patient had one sample above LOQ at day 30 and the other patient had four plasma samples above LOQ on both days 1 and 15, which ranged from 0.102 and 0.131 ng/mL. Due to the limited number of available data points, PK analysis was not undertaken.

Distribution: Classical plasma protein binding techniques were not feasible for adapalene due to the physiochemical properties of the molecule. However, an alternative method was adopted which measures the partitioning of the drug between plasma or protein solutions and erythrocytes. When ³H-adapalene was incubated with human whole blood, 26% was bound to erythrocytes and total binding of adapalene in blood was > 99%. Adapalene bound primarily to lipoproteins and human serum albumin.

Metabolism: Following 24-hour incubation with human hepatocytes, more than 90% of adapalene has been metabolized. Both metabolites and adapalene showed a possibility for conjugation - predominantly glucuronidation and sulfatation.

Excretion: Excretion appears to be primarily by the biliary route. The majority of an administered dose of 0.3% gel was excreted by 144 hours post dose and no drug was detected after the 6th day following last application. Under maximized conditions, the mean total

unchanged drug substance excreted in the faeces was 0.07% ∇ 0.06% of the total dose applied (range, 0.02% to 0.19%).

STORAGE AND STABILITY

DIFFERIN (adapalene) topical cream, gel and lotion, and DIFFERIN XP (adapalene) topical gel should be stored at room temperature (15° to 30°C). Keep from freezing. Keep container tightly closed. Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DIFFERIN (adapalene) topical cream, 0.1% w/w is supplied in the following sizes:

60 g laminate tube

Each gram of DIFFERIN topical cream contains adapalene 0.1% w/w (1 mg) in a vehicle consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl gluceth-20 sesquistearate, methyl glucose sesquistearate, methylparaben, phenoxyethanol, propylparaben, squalane, trolamine, and purified water.

DIFFERIN (adapalene) topical gel, 0.1% w/w is supplied in the following sizes:

60 g laminate tube

Each gram of DIFFERIN topical gel contains adapalene 0.1% w/w (1 mg) in a vehicle consisting of carbomer 940, edetate disodium, methylparaben, poloxamer 182, propylene glycol, sodium hydroxide and/or hydrochloric acid for pH adjustment, and purified water.

DIFFERIN (adapalene) topical lotion, 0.1% w/w is supplied in the following sizes:

60 mL HDPE bottle with pump
120 mL HDPE bottle with pump

Each gram of DIFFERIN topical lotion contains adapalene 0.1% w/w (1 mg) in a vehicle consisting of 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.

DIFFERIN XP (adapalene) topical gel, 0.3% w/w is supplied in the following sizes:

60 g laminate tube

Each gram of DIFFERIN XP topical gel contains adapalene 0.3% w/w (3 mg) in a vehicle consisting of carbomer homopolymer type C, edetate disodium, methylparaben, poloxamer 124,

propylene glycol, sodium hydroxide and/or hydrochloric acid for pH adjustment, and purified water.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

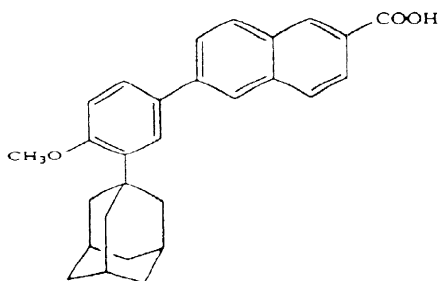
Drug Substance

Proper Name: adapalene

Chemical Name: 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

Molecular Formula and Molecular Mass: $C_{28}H_{28}O_3$; 412.52

Structural Formula:



Physicochemical properties: Adapalene is a white to off-white powder, which is sparingly soluble in tetrahydrofuran and practically insoluble in water and ethanol (96%).

CLINICAL TRIALS

Study demographics and trial design

Table 4: Summary of patient demographics for North American Phase III active- and vehicle-controlled clinical trial in *acne vulgaris*

Study #	Trial design	Dosage , route of administration, and duration	Study subjects (n=number)	Mean age (Range) Years	Gender % M/F
RD.06.SRE.18081	Double-blind, parallel, controlled (active & vehicle)	0.3% adapalene gel 0.1% adapalene gel gel vehicle Topical 12 weeks	(653) 258 261 134	18.2 (12 - 52)	49.5/50.5
RD.06.SPR.18113 and RD.06.SPR.18114	Double-blind, parallel, controlled (active & vehicle)	0.1% adapalene lotion lotion vehicle Topical 12 weeks	1068 1073	19.3 (12 - 54) 19.0 (12 - 64)	45.4/54.6 47.6/52.4
9111-CD271C-EV	Parallel, Randomized, Double-blind, Controlled (active & vehicle)	0.1% adapalene cream cream vehicle Topical 12 weeks	(350) 175 175	19 (12 - 31)	59/41

Male and female subjects, 12 years of age or older, were eligible to enroll in these controlled clinical trials. In study RD.06.SRE.18081, subjects with *acne vulgaris* with 20 to 50 inflammatory and 20 to 100 non-inflammatory lesions and no nodules or cysts were eligible to enroll in this study. In study RD.06.SPR.18113 and study RD.06.SPR.18114 with adapalene lotion 0.1%, patients with 20 to 50 inflammatory lesions on the face and 30 to 100 non-inflammatory lesions on the face, with no cysts and no more than one nodule on the face were eligible for enrollment. Subjects in study RD.06.SPR.18113 and study RD.06.SPR.18114 also had an Investigator's Global Assessment score of 3 (moderate) or 4 (severe) at Baseline.

Table 5: Summary of patient demographics for European Phase III active-controlled clinical trial in *acne vulgaris*

Study #	Trial design	Dosage , route of administration, and duration	Study subjects (n=number)	Mean age (Range) Years	Gender % M/F
RD.03.SRE.2673	Double-blind, parallel, active-controlled	0.3% adapalene gel 0.1% adapalene gel Topical 12 weeks	(418) 208 210	19.1 (12 - 39)	40.0/60.0

Male and female subjects, 12 years of age or older, were eligible to enroll in this controlled clinical trial. In study RD.03.SRE.2673, subjects with *acne vulgaris* with 15 to 50 inflammatory and 30 to 200 non-inflammatory lesions and a maximum of two nodules / cysts were eligible to enroll in this study.

Study results

Table 6: Results of North American Study RD.06.SRE.18081 in *acne vulgaris* at Week 12 (Observed)

Primary Endpoints*	Adapalene Gel, 0.3% (n=227)	Adapalene Gel, 0.1% (n=237)	Gel Vehicle (placebo) (n=120)
Success rate [% of subjects with "Clear" or "Almost Clear" on Investigator's Global Assessment (IGA)]	23.3% [p value vs 0.1%: 0.072] [p value vs vehicle: 0.002]	16.97%	10.0%
Median % lesion count reduction			
Total	-55.60 [p value vs 0.1%: 0.003] [p value vs vehicle: <0.001]	-48.25	-36.40
Inflammatory	-62.50 [p value vs 0.1%: 0.099] [p value vs vehicle: <0.001]	-57.80	-47.25
Non-inflammatory	-52.10 [p value vs 0.1%: 0.003] [p value vs vehicle: <0.001]	-43.45	-29.35

*CMH analysis

Table 7: Results of North American Studies RD.06.SPR.18113 and RD.06.SPR.18114 (combined) in *acne vulgaris* at Week 12 (LOCF, ITT)

Primary Endpoints	Adapalene Lotion 0.1% (n=1068)	Lotion Vehicle (n=1073)	p-value
Success Rate [% of patients with a Week 12 Investigator's Global Assessment (IGA) at least 2 grades lower than Baseline]	25.2%	16.9%	p<0.001 ^a
Mean absolute (percent) reduction from Baseline in lesion counts:			
Inflammatory	13.7 (-50.5%)	10.4 (-38.6%)	p<0.001 ^b
Non-inflammatory	21.4 (-46.4%)	14.6 (-33.0%)	p<0.001 ^b
Total	35.2 (-48.0%)	25.0 (-35.0%)	p<0.001 ^b

^a Cochran-Mantel-Haenszel test, stratified by analysis centre

^b ANCOVA (ranked and unranked)

Table 8: Results of European Study RD.03.SRE.2673 in *acne vulgaris* at Week 12 (Observed)

Primary Endpoints	Adapalene Gel, 0.3% (ITT n=208)	Adapalene Gel, 0.1% (ITT n=210)
Median % lesion count reduction		
Total	-67.1% [p value vs 0.1%: 0.134]	-61.4%
Inflammatory	-65.4% [p value vs 0.1%: 0.310]	-64.0%
Non-inflammatory	-68.8% [p value vs 0.1%: 0.145]	-60.0%

Table 9: Results of North American Study 9111-CD271C-EV in *acne vulgaris* at Week 12 (Observed)

Primary Endpoints	Adapalene Cream, 0.1% (n=162)	Vehicle Cream (n=167)
Mean % lesion count reduction		
Total	-32% [p value vs vehicle: 0.0001]	-15%
Inflammatory	-15% [p value vs vehicle: 0.2396]	-5%
Non-inflammatory	-37% [p value vs 0.05%: 0.0001]	-15%

DETAILED PHARMACOLOGY

Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a potent modulator of cellular differentiation, keratinization and inflammatory processes all of which represent important features in the pathology of *acne vulgaris*. Mechanistically, adapalene binds to specific retinoic 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. Studies in acne patients provide clinical evidence that topical adapalene is effective in reducing the noninflammatory acne lesions (open and closed comedones). Adapalene inhibits the chemotactic (directional) and chemokinetic (random) responses of human polymorphonuclear leucocytes in *in vitro* assay models; it also inhibits the metabolism of arachidonic acid, by lipoxidation, to inflammatory mediators. This profile suggests that the cell mediated inflammatory component of acne is modified by adapalene. Studies in human patients provide clinical evidence that topical adapalene is effective in reducing the inflammatory components of acne (i.e., papules and pustules).

Human Pharmacology

Pharmacokinetics

In vitro studies

In vitro experiments on human skin showed that skin is an effective barrier to adapalene penetration. The total amount of adapalene that penetrated into the skin accounted for 1.54% ± 0.22 of a finite applied dose of DIFFERIN Lotion, 0.1%. No detectable adapalene levels were seen in the receptor fluid. The skin penetration of adapalene from the 0.1% lotion was found in

vitro to be higher than with DIFFERIN 0.1% Cream ($0.64\% \pm 0.11$) but lower than with DIFFERIN 0.1% Gel ($2.75\% \pm 0.39$).

Pharmacodynamics

A clinical study in healthy subjects showed that Adapalene Vehicle Lotion and Adapalene Lotion, 0.1% had mean calculated cumulative irritancy indices of 0.37 and 0.58, respectively. The positive control (Sodium Lauryl Sulfate) and the negative control (White Petrolatum) had mean calculated cumulative irritancy indices of 2.86 and 0.38, respectively. The mean cumulative irritancy index scores of Adapalene Vehicle Lotion, Adapalene Lotion, 0.1% and the negative control are indicative of test articles with a mild irritation profile. The mean cumulative irritancy index score of the positive control is indicative of a cumulative irritant.

An additional clinical study in healthy subjects showed that Adapalene Lotion, 0.1% had a mean calculated cumulative irritancy index of 0.31, which is indicative of a test article with a mild irritation profile. Additionally, the reactivity observed with Adapalene Lotion, 0.1% was not considered evidence of induced contact sensitization.

TOXICOLOGY

Acute and Chronic Studies: The acute oral LD₅₀ of adapalene in Sprague-Dawley rats and in Charles River CD1 mice was found to be greater than 5000 mg/kg. The acute LD₅₀ of adapalene 0.3% gel or solution was found to be greater than 6 mg/kg in Sprague-Dawley rats (topical) and greater than 30 mg/kg in Iffa Credo OF1 mice (oral), respectively. No pharmacotoxic effects were observed in these studies.

Systemic administration of adapalene produced a hypervitaminosis A syndrome in mice, rats and dogs. In rats, it was present after four weeks at 5 mg/kg with adapalene given orally by dietary administration. The main target organ appears to be the bone.

Slight decreases in red blood cell parameters were observed in all species where adapalene was given orally. These slight changes were also observed in some topical studies in rats and rabbits, and occurred mainly with adapalene at 0.3% solution or aqueous gel. No morphological or histopathological changes were observed in bone marrow in several oral studies in rats and topical studies in rats and rabbits for periods up to six months. It is concluded that these changes were peripheral rather than central. The dose producing these minimal changes corresponds to 17 times the MRHD of adapalene 0.3% gel based on mg/m² comparisons for rats and 32 times the MRHD for rabbits.

Changes in clinical chemistry parameters (mostly decreases in protein and albumin concentrations, and increases in triglyceride concentration and liver-specific alkaline phosphatase activity) were observed in animals when adapalene was administered dermally (rats) or orally (rats and dogs). The effects were dose related, but reversible in recovery studies.

Given topically in solution (rabbits) or in aqueous gel (rabbits and mice), adapalene gave slight to

moderate irritation according to the concentration and the duration and frequency of treatment.

Following 26 weeks of daily cutaneous application to rats at concentrations of up to 0.3% (6 mg/kg/day), adapalene gel was well tolerated. The dose related changes observed included erythema, flaking, and acanthosis at the application site, all of which were reversible over the course of an 8 week recovery period.

Adapalene lotion 0.1%, at doses up to 1.2 mg/kg/day, was applied to the skin of minipigs in a 3-month dermal toxicity study with toxicokinetic analysis. Most of the treatment-related effects were of a local dermal nature including very slight erythema with very slight or slight edema to minimal eschar formation. These mild signs of skin irritation essentially disappeared by the end of the one month recovery period. There were no signs of systemic toxicity. No significant plasma levels of drug were observed on day 1, and after 91 days of repeated application, plasma levels were noted in some of the animals in the 0.2 mg/kg/day group and in most of the animals in the 0.6 and 1.2 mg/kg/day groups, although levels were very variable. Plasma steady-state levels were probably not reached in all animals by day 91. The NOAEL for this study was considered to be the high dose of 1.2 mg/kg/day.

Carcinogenicity Studies: Lifetime studies with adapalene have been completed in mice at topical doses of 0.6 (0.03%), 2 (0.1%) and 6 (0.3%) 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. However, a high incidence of splenic extra-medullary haematopoiesis was observed in male mice treated with 6 mg/kg/day (0.3%) topically applied adapalene gel. Oral administration of adapalene to Sprague-Dawley rats at a dose of 1.5 mg/kg/day for two years resulted in a higher incidence in males, relative to controls, of benign pheochromocytoma of the adrenal medulla. These neoplastic changes are considered to have no relevance to the topical use of adapalene in humans in clinical conditions.

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.

Mutagenicity Studies: In a series of *in vivo* and *in vitro* tests, adapalene did not demonstrate any mutagenic or genotoxic activity.

Reproductive and Teratology Studies: Adapalene administered orally at doses of ≥ 25 mg/kg/day can induce major structural changes including cleft palate, cranial abnormalities and spina bifida in rat and rabbit foetuses. Similar teratogenic effects have also been reported with other retinoids.

In the topical studies at the clinical concentration of 0.3% (equivalent to 6 mg/kg/day of applied adapalene, and corresponding to 17 times the MRHD for rats or 32 times the MRHD for rabbits), increases in additional foetal rib numbers were recorded in both rats and rabbits. In the rat, there were also other minimal increases in skeletal anomalies such as small additional fissure in the parietal bone and asymmetric pelvis. In the rabbit, the skeletal anomalies were small additional

fissures in the inter-parietal bone, 27 pre-sacral vertebrae, incomplete ossification of the head of limb long bones, and tail anomalies.

In the topical studies at the clinical concentration of 0.1% (equivalent to 2 mg/kg/day of applied adapalene), no adverse effects were observed in rabbits and only a marginal increase in the incidence of rudimentary additional lumbar ribs in rats was observed. The doses used in the topical teratology studies correspond to about 51 and 96 times the MRHD of adapalene 0.1% in the rat and rabbit respectively.

No effects of adapalene (doses up to 20 mg/kg/day) were found in rats on the reproductive performance or fertility of the F₀ males or females. Total litter loss was suffered by 3 out of 25 F₀ female rats (12%) orally dosed at 15 mg/kg/day; these females had pale and inactive mammary tissues. There were no detectable effects on the growth, development and subsequent reproductive function of the F₁ offspring.

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PART III: CONSUMER INFORMATION

PrDIFFERIN®
adapalene topical cream
0.1% w/w
adapalene topical gel
0.1% w/w
adapalene topical lotion
0.1% w/w
PrDIFFERIN XP®
adapalene topical gel
0.3% w/w

This leaflet is part III of a three-part "Product Monograph" published when DIFFERIN and DIFFERIN XP were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DIFFERIN and DIFFERIN XP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- treating acne in patients 12 years of age and older.

What it does:

DIFFERIN and DIFFERIN XP is believed to work by modifying the action of skin cells to produce fewer pimples.

When it should not be used:

- If you are pregnant or planning a pregnancy.
- You are allergic to adapalene or any of the other ingredients (see **What the important nonmedicinal ingredients are:**) or components of the packaging. Check with your doctor if you know you are allergic to certain ingredients or package components to ensure that you can use DIFFERIN or DIFFERIN XP.
- If you have eczema or very irritated skin (such as seborrheic dermatitis)

What the medicinal ingredient is:

adapalene

What the nonmedicinal ingredients are:

DIFFERIN 0.1% w/w Cream:

Carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl gluceth 20 sesquistearate, methyl glucose sesquistearate, methylparaben, phenoxyethanol, propylparaben, squalane, trolamine, and purified water.

DIFFERIN 0.1% w/w Gel:

Carbomer 940, edetate disodium, methylparaben, poloxamer 182, propylene glycol, sodium hydroxide and/or hydrochloric acid for pH adjustment, and purified water.

DIFFERIN 0.1% w/w Lotion:

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.

DIFFERIN XP 0.3% w/w Gel:

Carbomer Homopolymer Type C, edetate disodium, methylparaben, poloxamer 124, propylene glycol, sodium hydroxide and/or hydrochloric acid for pH adjustment, and purified water.

For a full listing of nonmedicinal ingredients see Part I of the product monograph.

What dosage forms it comes in:

DIFFERIN 0.1% w/w Cream in a 60 g tube

DIFFERIN 0.1% w/w Gel in a 60 g tube

DIFFERIN 0.1% w/w Lotion in a 60 mL and 120 mL bottle with pump.*

DIFFERIN XP 0.3% w/w Gel in a 60 g tube.

**DIFFERIN Lotion not currently marketed in Canada.*

WARNINGS AND PRECAUTIONS

If you are pregnant, or planning a pregnancy you should discontinue use of DIFFERIN or DIFFERIN XP. If you are a female of childbearing years, you should use DIFFERIN or DIFFERIN XP only after consulting your doctor about contraceptive counselling.

BEFORE you use DIFFERIN or DIFFERIN XP talk to your doctor or pharmacist if:

- You are breast feeding or intending to breast feed. It is not known if this drug is passed into breast milk. To avoid contact exposure of the infant, do not apply DIFFERIN or DIFFERIN XP to the chest when used during breast-feeding.
- You are using any other acne medications. DIFFERIN and DIFFERIN XP should not be used with other acne medications unless your doctor recommends them.
- You are using any other prescription or OTC (over the counter) drugs or herbal remedies.

Many of the medicines used to treat acne can make a person more likely to sunburn. So, exposure to too much sunlight, including sunlamps, should be avoided while using DIFFERIN or DIFFERIN XP. If you must be out in the sun, use a good sunscreen product (SPF 15 or higher) designed not to clog pores (non-comedogenic) and protective clothing over the treated areas.

Do not use "waxing" as a way of removing unwanted hair in the areas where you will be applying DIFFERIN or DIFFERIN XP, as this may increase your skin sensitivity.

Avoid using oily makeup or creams, or products that make your skin dry or peel, or cause irritation such as abrasive soaps or cleansers, astringents, alcohol or those containing spices or limes. These may make your acne worse.

INTERACTIONS WITH THIS MEDICATION

Drug-Drug Interactions

As DIFFERIN and DIFFERIN XP may cause local irritation, it is possible that use of abrasive cleansers, strong drying agents, or irritant products at the same time may produce increased irritation. You should take particular care when using preparations containing sulfur, resorcinol, or salicylic acid with DIFFERIN or DIFFERIN XP. If these preparations have been used, you should wait to start therapy with DIFFERIN until the effects of such preparations have lessened.

On the advice of your doctor, other topical anti-acne treatments (e.g., erythromycin topical solution, clindamycin phosphate topical solution 1% or benzoyl peroxide products in concentrations up to 10%) may be used in the morning when DIFFERIN or DIFFERIN XP is used at night.

Drug-Herb Interactions

Interactions with herbal products have not been established.

PROPER USE OF THIS MEDICATION

Usual dose:

Use DIFFERIN or DIFFERIN XP once a day at night before you go to bed. You should first wash your face with a gentle cleanser and blot it dry with a soft towel -- do not rub your face. Then, apply a thin film of DIFFERIN or DIFFERIN XP to the areas where you have acne. Usually, four pea-sized amounts of DIFFERIN cream or gel, or DIFFERIN XP should be enough to cover your entire face. For DIFFERIN lotion, dispense a nickel size amount (3 - 4 actuations of the pump) to cover your entire face. DO NOT SPOT APPLY - cover the entire affected area.

Keep DIFFERIN or DIFFERIN XP away from your eyes, lips, the corners of your nose and mucous membranes. If you get any in your eyes, flush your eyes with clean warm water right away. This medication should not be applied to cuts, abrasions, eczematous (skin with a red, itchy rash) or sunburned skin.

Use only the amount your doctor recommends. Using more DIFFERIN or DIFFERIN XP will not make it work better or faster.

Your acne should improve in 4-8 weeks and you should see more improvement as you continue to use DIFFERIN or DIFFERIN XP.

Overdose:

DIFFERIN or DIFFERIN XP is meant to be applied in a thin film only on the areas of your skin where you have acne. If too much medication is applied, you will not get faster or better results. Instead, you may see a lot of redness or peeling, and your skin may feel hot or burning.

A 60 gram tube of DIFFERIN XP contains a total of 180 mg of adapalene. Even if someone eats the contents of a full tube of DIFFERIN or DIFFERIN XP, there is not enough active ingredient to cause serious toxicity. However, you should still contact your poison control centre, and if you are a woman of childbearing age, have a pregnancy test done.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, it is not necessary to make up the missed dose. Just wait until the next evening and use DIFFERIN or DIFFERIN XP as usual. Apply the same amount as you usually would. Do not apply extra.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Do not be discouraged if DIFFERIN or DIFFERIN XP causes some redness, skin burning sensation or peeling when you first start to use it (2-4 weeks). This happens when your skin is adjusting to DIFFERIN or DIFFERIN XP's action of unplugging clogged pores. If these problems continue to happen or if they are getting worse, talk to your doctor. He/she may suggest that you use a moisturizer, or he/she may recommend a change in your dose, or in how often you use the medication. DIFFERIN or DIFFERIN XP may also cause skin irritation, dry skin, skin discomfort, pain or swelling of skin, itching, acne, dermatitis contact or allergic, or may make you more likely to sunburn.

If DIFFERIN or DIFFERIN XP gets in your eye, rinse it out promptly with lots of water. Contact with your eye may cause swelling, conjunctivitis and eye irritation. If the irritation persists, talk to your doctor. DIFFERIN or DIFFERIN XP may cause eyelid irritation, itching, redness or swelling.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Skin becomes very dry, red, swollen, or blistered			√

This is not a complete list of side effects. For any unexpected effects while taking DIFFERIN or DIFFERIN XP, contact your doctor or pharmacist.

HOW TO STORE IT

DIFFERIN or DIFFERIN XP should be stored at room temperature (15 to 30°C). Protect from freezing. Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
 - **Fax toll-free to 1-866-678-6789, or**
 - **Mail to: Canada Vigilance Program**
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Galderma Canada Inc., at: 1-800-467-2081 or visit our website at www.galderma.ca.

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